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     FILE 'REGISTRY' ENTERED AT 17:14:48 ON 31 AUG 2004
L1             2 S ATRASENTAN
L2             1 S 195733-43-8/RN
L3             0 S 19570407204/RN
L4             1 S 195704-72-4/RN
L5             1 S 178738-96-0/RN
L6             1 S 173937-92-3/RN
L7             1 S 173937-91-2/RN
L8             1 S 173864-34-1
L9             1 S 173864-01-2/RN

=> s l1 or l2 or l4 or l5 or l6 or l7 or l8 or l9
L10            7 L1 OR L2 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9

=> file caplus uspatfull biotechno ipa biosis embase toxcenter medline cancerlit
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                     ENTRY    SESSION
FULL ESTIMATED COST                                 17.95      18.16

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FILE 'MEDLINE' ENTERED AT 17:20:21 ON 31 AUG 2004

FILE 'CANCERLIT' ENTERED AT 17:20:21 ON 31 AUG 2004

=> d his

     (FILE 'HOME' ENTERED AT 17:14:39 ON 31 AUG 2004)

     FILE 'REGISTRY' ENTERED AT 17:14:48 ON 31 AUG 2004
L1             2 S ATRASENTAN
L2             1 S 195733-43-8/RN
L3             0 S 19570407204/RN
L4             1 S 195704-72-4/RN
L5             1 S 178738-96-0/RN
L6             1 S 173937-92-3/RN
L7             1 S 173937-91-2/RN
L8             1 S 173864-34-1
L9             1 S 173864-01-2/RN
L10            7 S L1 OR L2 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9

     FILE 'CAPLUS, USPATFULL, BIOTECHNO, IPA, BIOSIS, EMBASE, TOXCENTER,
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     MEDLINE, CANCERLIT' ENTERED AT 17:20:21 ON 31 AUG 2004

=> s l10
L11         581 L10

=> s bone# metasta?
L12       31827 BONE# METASTA?

=> s osteoblast?
L13       81268 OSTEOBLAST?

=> d his

     (FILE 'HOME' ENTERED AT 17:14:39 ON 31 AUG 2004)

     FILE 'REGISTRY' ENTERED AT 17:14:48 ON 31 AUG 2004
L1             2 S ATRASENTAN
L2             1 S 195733-43-8/RN
L3             0 S 19570407204/RN
L4             1 S 195704-72-4/RN
L5             1 S 178738-96-0/RN
L6             1 S 173937-92-3/RN
L7             1 S 173937-91-2/RN
L8             1 S 173864-34-1
L9             1 S 173864-01-2/RN
L10            7 S L1 OR L2 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9

     FILE 'CAPLUS, USPATFULL, BIOTECHNO, IPA, BIOSIS, EMBASE, TOXCENTER,
     MEDLINE, CANCERLIT' ENTERED AT 17:20:21 ON 31 AUG 2004
L11          581 S L10
L12        31827 S BONE# METASTA?
L13        81268 S OSTEOBLAST?

=> s l11 and l12
L14          30 L11 AND L12

=> s l11 and l13
L15           9 L11 AND L13

=> s l14 and l15
L16           8 L14 AND L15

=> duplicate remove l8
DUPLICATE IS NOT AVAILABLE IN 'REGISTRY'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                     ENTRY    SESSION
FULL ESTIMATED COST                                  13.58      31.74

FILE 'REGISTRY' ENTERED AT 17:23:12 ON 31 AUG 2004
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STRUCTURE FILE UPDATES:   30 AUG 2004  HIGHEST RN 736108-36-4
DICTIONARY FILE UPDATES:  30 AUG 2004  HIGHEST RN 736108-36-4

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

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http://www.cas.org/ONLINE/DBSS/registryss.html
PROCESSING COMPLETED FOR L8
L17 1 DUPLICATE REMOVE L8 (0 DUPLICATES REMOVED)

=> d l16 1-8 bib abs
YOU HAVE REQUESTED DATA FROM FILE 'USPATFULL, BIOTECHNO, BIOSIS, EMBASE' -
CONTINUE? (Y)/N:y

L16 ANSWER 1 OF 8 USPATFULL on STN
AN 2002:106248 USPATFULL
TI Methods of treating cancer and the pain associated therewith using endothelin antagonists
IN Janus, Todd J., Gurnee, IL, UNITED STATES
Padley, Robert J., Lake Bluff, IL, UNITED STATES
PI US 2002055457 A1 20020509
AI US 2001-923616 A1 20010806 (9)
PRAI US 2000-223486P 20000807 (60)
DT Utility
FS APPLICATION
LREP Steven F. Weinstock, Abbott Laboratories, D-377/AP6D, 100 Abbott Park Road, Abbott Park, IL, 60064-6050
CLMN Number of Claims: 58
ECL Exemplary Claim: 1
DRWN 7 Drawing Page(s)
LN.CNT 1394
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The instant invention is directed to methods for the inhibition of **bone metastases**, methods for the prevention of growth of new metastases, methods for the inhibition of bone turnover, and methods for the prevention of bone loss in patients, including cancer patients, using an endothelin ET-A receptor antagonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 2 OF 8 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN
AN 2003:37140134 BIOTECHNO
TI A causal role for endothelin-1 in the pathogenesis of **osteoblastic bone metastases**
AU Yin J.J.; Mohammad K.S.; Kakonen S.M.; Harris S.; Wu-Wong J.R.; Wessale J.L.; Padley R.J.; Garrett I.R.; Chirgwin J.M.; Guise T.A.
CS T.A. Guise, Department of Internal Medicine, Division of Endocrinology, University of Virginia, P.O. Box 801419, Charlottesville, VA 22908, United States.
E-mail: tag4n@virginia.edu
SO Proceedings of the National Academy of Sciences of the United States of America, (16 SEP 2003), 100/19 (10954-10959), 42 reference(s)
CODEN: PNASA6 ISSN: 0027-8424
DT Journal; Article
CY United States
LA English
SL English
AB **Osteoblastic bone metastases** are common in prostate and breast cancer patients, but mechanisms by which tumor cells stimulate new bone formation are unclear. We identified three breast cancer cell lines that cause **osteoblastic** metastases in a mouse model and secrete endothelin-1. Tumor-produced endothelin-1 stimulates

new bone formation in vitro and **osteoblastic** metastases in vivo via the endothelin A receptor. Treatment with an orally active endothelin A receptor antagonist dramatically decreased **bone metastases** and tumor burden in mice inoculated with ZR-75-1 cells. Tumor-produced endothelin-1 may have a major role in the establishment of **osteoblastic bone metastases**, and endothelin A receptor blockade represents effective treatment.

L16 ANSWER 3 OF 8 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2003:125326 BIOSIS
DN PREV200300125326
TI Role of endothelin-1 in **osteoblastic bone metastases**.
AU Guise, Theresa A. [Reprint Author]; Yin, Juan Juan; Mohammad, Khalid S.
CS Department of Medicine, Division of Endocrinology and Metabolism, University of Virginia, Aurbach Medical Research Building, PO Box 801419, Charlottesville, VA, 22908, USA
tag4n@virginia.edu
SO Cancer, (February 1 2003) Vol. 97, No. 3 Supplement, pp. 779-784. print.
ISSN: 0008-543X (ISSN print).
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 5 Mar 2003
Last Updated on STN: 5 Mar 2003
AB BACKGROUND: Certain solid tumors metastasize to bone and cause an **osteoblastic** response. The mechanisms by which tumor cells stimulate this new bone formation are not completely understood. METHODS: The authors identified three breast cancer lines that cause **osteoblastic** metastases in female nude mice and provided evidence that tumor-produced endothelin-1 (ET-1) mediates the **osteoblastic** response. RESULTS: Tumor conditioned media, as well as exogenous ET-1, stimulated **osteoblast** proliferation and new bone formation in cultures of mouse calvariae. These effects were blocked by antagonists of the endothelin A (ETA), but not ETB, receptors. Mice inoculated with the ZR-75-1 breast cancer line and treated with a selective ETA receptor antagonist (ABT-627) had significantly fewer **osteoblastic bone metastases** and less tumor burden compared with untreated mice. In contrast, there was no effect of ABT-627 on osteolytic **bone metastases** caused by ET-1-negative breast cancer, MDA-MB-231. ABT-627 had no effect on growth in vitro or at the orthotopic site of ZR-75-1 or MDA-MB-231 cells. CONCLUSIONS: Collectively, the data suggested that tumor-produced ET-1 mediates **osteoblastic bone metastases** by stimulating **osteoblast** proliferation and new bone formation. ETA receptor blockade may be useful for prevention and the treatment of **osteoblastic bone metastases** due to breast or prostate cancer.

L16 ANSWER 4 OF 8 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2002:394721 BIOSIS
DN PREV200200394721
TI Endothelin-1 dependent and independent mechanisms concur in the increased bone mass of prostate cancer **bone metastases**.
AU Yang, Jun [Reprint author]; Fizazi, Karim; Peleg, Sara; Sikes, Charles R.; Raymond, Austin K.; Vazquez, Elba S.; Daliani, Danai; Janus, Todd; Logothetis, Christopher J.; Karsenty, Gerard; Navone, Nora M.
CS MD Anderson Cancer Center, Houston, TX, USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2002) Vol. 43, pp. 315. print.
Meeting Info.: 93rd Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA. April 06-10, 2002.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LA English
ED Entered STN: 24 Jul 2002
Last Updated on STN: 24 Jul 2002

L16 ANSWER 5 OF 8 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2002:142771 BIOSIS
DN PREV200200142771
TI Endothelin-1 (ET-1) mediates pathological but not normal bone remodeling.
AU Mohammad, K. S. [Reprint author]; Yin, J. J.; Grubbs, B. G.; Cui, Y.; Padley, R.; Guise, T. A.
CS Medicine/Endocrinology, UTHSCSA, San Antonio, TX, USA
SO Breast Cancer Research and Treatment, (October, 2001) Vol. 69, No. 3, pp. 212. print.
Meeting Info.: 24th Annual San Antonio Breast Cancer Symposium. San Antonio, Texas, USA. December 10-13, 2001.
CODEN: BCTRD6. ISSN: 0167-6806.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 14 Feb 2002
Last Updated on STN: 26 Feb 2002

L16 ANSWER 6 OF 8 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2001:406611 BIOSIS
DN PREV200100406611
TI The effects of endothelin-1 and Abt-627, an endothelin-1 antagonist, in an in vitro model of **bone metastases** from prostate cancer.
AU Fizazi, Karim [Reprint author]; Yang, Jun [Reprint author]; Daliani, Danai [Reprint author]; Logothetis, Christopher [Reprint author]; Peleg, Sara [Reprint author]; Navone, Nora M. [Reprint author]
CS MD Anderson Cancer Center, Houston, TX, USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2001) Vol. 42, pp. 231. print.
Meeting Info.: 92nd Annual Meeting of the American Association for Cancer Research. New Orleans, LA, USA. March 24-28, 2001. American Association for Cancer Research.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 22 Aug 2001
Last Updated on STN: 22 Feb 2002

L16 ANSWER 7 OF 8 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2003435088 EMBASE
TI Mechanisms of **Osteoblastic** Metastases: Role of Endothelin-1.
AU Mohammad K.S.; Guise T.A.
CS Dr. T.A. Guise, University of Virginia, Department of Internal Medicine, Div. of Endocrinology and Metabolism, 450 Ray C. Hunt Drive, Charlottesville, VA 22903, United States. TAG4N@Virginia.edu
SO Clinical Orthopaedics and Related Research, (2003) -/415 SUPPL. (S67-S74). Refs: 67
ISSN: 0009-921X CODEN: CORTBR
CY United States
DT Journal; Conference Article
FS 016 Cancer
029 Clinical Biochemistry
033 Orthopedic Surgery
LA English
SL English
AB Certain solid tumors metastasize to bone, causing an **osteoblastic** response. The mechanisms by which tumor cells stimulate this new bone

formation are not understood completely. We identified three breast cancer lines that cause **osteoblastic** metastases in female nude mice and provide evidence that tumor-produced endothelin-1 (ET-1) mediates the **osteoblastic** response. Tumor-conditioned media and exogenous ET-1 stimulated **osteoblast** proliferation and new bone formation in cultures of calvarias from mice. These effects were blocked by endothelin A (ET(A)) but not by ET(B) receptor antagonists. Mice inoculated with the ZR-75-1 breast cancer line and treated with a selective ET(A) receptor antagonist (ABT-627) had significantly fewer **osteoblastic bone metastases** and less tumor burden compared with untreated mice. In contrast, there was no effect of ABT-627 on osteolytic **bone metastases** caused by ET-1-negative breast cancer, MDA-MB-231. ABT-627 had no effect on cell growth in vitro or at the orthotopic site (mammary fat pad) of ZR-75-1, or MDA-MB-231 cells. Collectively, the data suggest that tumor-produced ET-1 mediates **osteoblastic bone metastases** by stimulating **osteoblast** proliferation and new bone formation. Endothelin A receptor blockade may be useful for the prevention and treatment of **osteoblastic bone metastases** attributable to breast or prostate cancer.

L16 ANSWER 8 OF 8 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2003379832 EMBASE
TI A causal role for endothelin-1 in the pathogenesis of **osteoblastic bone metastases**.
AU Yin J.J.; Mohammad K.S.; Kakonen S.M.; Harris S.; Wu-Wong J.R.; Wessale J.L.; Padley R.J.; Garrett I.R.; Chirgwin J.M.; Guise T.A.
CS T.A. Guise, Department of Internal Medicine, Division of Endocrinology, University of Virginia, P.O. Box 801419, Charlottesville, VA 22908, United States. tag4n@virginia.edu
SO Proceedings of the National Academy of Sciences of the United States of America, (16 Sep 2003) 100/19 (10954-10959).
Refs: 42
ISSN: 0027-8424 CODEN: PNASA6
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
016 Cancer
037 Drug Literature Index
LA English
SL English
AB **Osteoblastic bone metastases** are common in prostate and breast cancer patients, but mechanisms by which tumor cells stimulate new bone formation are unclear. We identified three breast cancer cell lines that cause **osteoblastic** metastases in a mouse model and secrete endothelin-1. Tumor-produced endothelin-1 stimulates new bone formation in vitro and **osteoblastic** metastases in vivo via the endothelin A receptor. Treatment with an orally active endothelin A receptor antagonist dramatically decreased **bone metastases** and tumor burden in mice inoculated with ZR-75-1 cells. Tumor-produced endothelin-1 may have a major role in the establishment of **osteoblastic bone metastases**, and endothelin A receptor blockade represents effective treatment.

=> d his

(FILE 'HOME' ENTERED AT 17:14:39 ON 31 AUG 2004)

FILE 'REGISTRY' ENTERED AT 17:14:48 ON 31 AUG 2004
L1 2 S ATRASENTAN
L2 1 S 195733-43-8/RN
L3 0 S 19570407204/RN

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L4             1 S 195704-72-4/RN
L5             1 S 178738-96-0/RN
L6             1 S 173937-92-3/RN
L7             1 S 173937-91-2/RN
L8             1 S 173864-34-1
L9             1 S 173864-01-2/RN
L10            7 S L1 OR L2 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9

     FILE 'CAPLUS, USPATFULL, BIOTECHNO, IPA, BIOSIS, EMBASE, TOXCENTER,
     MEDLINE, CANCERLIT' ENTERED AT 17:20:21 ON 31 AUG 2004
L11          581 S L10
L12        31827 S BONE# METASTA?
L13        81268 S OSTEOBLAST?
L14           30 S L11 AND L12
L15            9 S L11 AND L13
L16            8 S L14 AND L15

     FILE 'REGISTRY' ENTERED AT 17:23:12 ON 31 AUG 2004
L17            1 DUPLICATE REMOVE L8 (0 DUPLICATES REMOVED)

     FILE 'USPATFULL, BIOTECHNO, BIOSIS, EMBASE' ENTERED AT 17:23:43 ON 31 AUG
     2004

     FILE 'REGISTRY' ENTERED AT 17:23:44 ON 31 AUG 2004

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L34 NOT FOUND
The L-number entered could not be found.  To see the definition
of L-numbers, enter DISPLAY HISTORY at an arrow prompt (=>).

=> s l14 or l15
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           742 METASTA?
             0 BONE# METASTA?
                 (BONE#(W)METASTA?)
           283 OSTEOBLAST?
L18          0 L14 OR L15

=> d l14 1-30 bib abs
YOU HAVE REQUESTED DATA FROM FILE 'CAPLUS, USPATFULL, BIOTECHNO, BIOSIS, EMBASE,
TOXCENTER' - CONTINUE? (Y)/N:y



L14  ANSWER 1 OF 30  CAPLUS  COPYRIGHT 2004 ACS on STN
AN   2003:925734  CAPLUS
DN   139:390556
TI   Endothelin receptor antagonists in the treatment of prostate cancer
AU   Lassiter, Lance K.; Carducci, Michael A.
CS   Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD,
     21231, USA
SO   Seminars in Oncology (2003), 30(5), 678-688
     CODEN: SOLGAV; ISSN: 0093-7754
PB   W. B. Saunders Co.
DT   Journal; General Review
LA   English
AB   A review.  The endothelin (ET) axis represents a novel and exciting target
     in the treatment of prostate cancer.  ET-1, acting primarily through the
     endothelin A receptor (ETA), is integrally involved in multiple facets of
     prostate cancer progression, including cell growth, inhibition of
     apoptosis, angiogenesis, development and progression of bone
     metastases, and mediation of pain responses.  Clin. trials with
     the ETA antagonist, atrasentan, have demonstrated good tolerability, with
     the most common adverse events being headache, rhinitis, and peripheral
```

edema. These trials have demonstrated statistically significant improvements in pain measures, prostate-specific antigen (PSA) kinetics, biol. markers of bone changes, and development of **bone metastases**. There have also been consistent improvements in time to progression, although not always statistically significant. Ongoing studies in a variety of patient populations will better define the role of ET receptor antagonists in the treatment of men with prostate cancer. In this article, we review the biol. and pathophysiol. of the ET axis in prostate cancer, critically analyze the major clin. trials reported to date, and discuss some emerging data and how it may impact the way we proceed in the future with the development of this class of drugs in prostate cancer.

RE.CNT 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:124519 CAPLUS
DN 139:270402
TI Suppression of Prostate Cancer Induced Bone Remodeling by The Endothelin Receptor A Antagonist Atrasentan
AU Nelson, Joel B.; Nabulsi, Azmi A.; Vogelzang, Nicholas J.; Breul, Jurgen; Zonnenberg, Bernard A.; Daliani, Danai D.; Schulman, Claude C.; Carducci, Michael A.
CS Sidney Kimmel Comprehensive Cancer Cent., The Johns Hopkins Univ. Sch. Med., Baltimore, MD, USA
SO Journal of Urology (Hagerstown, MD, United States) (2003), 169(3), 1143-1149
CODEN: JOURAA; ISSN: 0022-5347
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB We examined the effects of atrasentan (endothelin-A receptor antagonist) on bone deposition and resorption markers and on bone scan index. This double-blind, randomized, placebo controlled clin. trial of hormone refractory prostate cancer patients was done at 74 medical centers in the United States and Europe. A total of 288 asymptomatic patients with hormone refractory prostate adenocarcinoma and evidence of metastatic disease were randomized to 1 of 3 treatment groups, namely 2.5 mg. atrasentan, 10 mg. atrasentan or placebo administered orally daily until disease progression. The main outcomes measures were changes in bone deposition markers (total alkaline phosphatase and bone alkaline phosphatase) and bone resorption (N-telopeptides, C-telopeptides and deoxypyridinoline), and in the bone scan index. At baseline markers of bone deposition and resorption were elevated 1.4 to 2.7-fold above resp. upper limits of normal. Subjects receiving placebo experienced a 58% elevation in mean total alkaline phosphatase and a 99% elevation in mean bone alkaline phosphatase ($p < 0.001$), whereas subjects receiving 10 mg. atrasentan maintained stable mean total alkaline phosphatase and bone alkaline phosphatase values compared with baseline. N-telopeptides, C-telopeptides and deoxypyridinoline elevation from baseline were consistently less in patients receiving 10 mg. atrasentan compared with placebo. Similar trends were observed in subjects who received 2.5 mg. atrasentan. Changes in clin. bone scan studies paralleled bone marker changes. Atrasentan suppressed markers of biochem. and **bone metastasis** and demonstrates clin. activity for hormone refractory prostate cancer.

RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:354070 CAPLUS
DN 136:350550

TI Methods of treating cancer and the pain associated therewith using endothelin antagonists
IN Janus, Todd J.; Padley, Robert J.
PA USA
SO U.S. Pat. Appl. Publ., 24 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002055457	A1	20020509	US 2001-923616	20010806
PRAI	US 2000-223486P	P	20000807		

OS MARPAT 136:350550
AB The instant invention is directed to methods for the inhibition of **bone metastases**, methods for the prevention of growth of new metastases, methods for the inhibition of bone turnover, and methods for the prevention of bone loss in patients, including cancer patients, using an endothelin ET-A receptor antagonist.

L14 ANSWER 4 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:122776 CAPLUS
DN 136:161346
TI Methods of treating cancer and the pain associated therewith using endothelin antagonists
IN Janus, Todd J.; Padley, Robert J.
PA Abbott Laboratories, USA
SO PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002011713	A2	20020214	WO 2001-US24716	20010806
	WO 2002011713	A3	20030717		
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2001081134	A5	20020218	AU 2001-81134	20010806
	EP 1347751	A2	20031001	EP 2001-959595	20010806
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2004520266	T2	20040708	JP 2002-517050	20010806
	NO 2003000593	A	20030206	NO 2003-593	20030206
	BG 107577	A	20031031	BG 2003-107577	20030221
PRAI	US 2000-633389	A	20000807		
	WO 2001-US24716	W	20010806		

OS MARPAT 136:161346
AB The instant invention is directed to methods for the inhibition of **bone metastases**, methods for the prevention of growth of new metastases, methods for the inhibition of bone turnover, and methods for the prevention of bone loss in patients, including cancer patients, using an endothelin ET-A receptor antagonist.

L14 ANSWER 5 OF 30 USPATFULL on STN
AN 2002:106248 USPATFULL
TI Methods of treating cancer and the pain associated therewith using

endothelin antagonists
IN Janus, Todd J., Gurnee, IL, UNITED STATES
Padley, Robert J., Lake Bluff, IL, UNITED STATES
PI US 2002055457 A1 20020509
AI US 2001-923616 A1 20010806 (9)
PRAI US 2000-223486P 20000807 (60)
DT Utility
FS APPLICATION
LREP Steven F. Weinstock, Abbott Laboratories, D-377/AP6D, 100 Abbott Park Road, Abbott Park, IL, 60064-6050
CLMN Number of Claims: 58
ECL Exemplary Claim: 1
DRWN 7 Drawing Page(s)
LN.CNT 1394
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The instant invention is directed to methods for the inhibition of **bone metastases**, methods for the prevention of growth of new metastases, methods for the inhibition of bone turnover, and methods for the prevention of bone loss in patients, including cancer patients, using an endothelin ET-A receptor antagonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 6 OF 30 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN
AN 2003:37140134 BIOTECHNO
TI A causal role for endothelin-1 in the pathogenesis of osteoblastic **bone metastases**
AU Yin J.J.; Mohammad K.S.; Kakonen S.M.; Harris S.; Wu-Wong J.R.; Wessale J.L.; Padley R.J.; Garrett I.R.; Chirgwin J.M.; Guise T.A.
CS T.A. Guise, Department of Internal Medicine, Division of Endocrinology, University of Virginia, P.O. Box 801419, Charlottesville, VA 22908, United States.
E-mail: tag4n@virginia.edu
SO Proceedings of the National Academy of Sciences of the United States of America, (16 SEP 2003), 100/19 (10954-10959), 42 reference(s)
CODEN: PNASA6 ISSN: 0027-8424
DT Journal; Article
CY United States
LA English
SL English
AB Osteoblastic **bone metastases** are common in prostate and breast cancer patients, but mechanisms by which tumor cells stimulate new bone formation are unclear. We identified three breast cancer cell lines that cause osteoblastic metastases in a mouse model and secrete endothelin-1. Tumor-produced endothelin-1 stimulates new bone formation in vitro and osteoblastic metastases in vivo via the endothelin A receptor. Treatment with an orally active endothelin A receptor antagonist dramatically decreased **bone metastases** and tumor burden in mice inoculated with ZR-75-1 cells. Tumor-produced endothelin-1 may have a major role in the establishment of osteoblastic **bone metastases**, and endothelin A receptor blockade represents effective treatment.

L14 ANSWER 7 OF 30 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN
AN 2003:36876616 BIOTECHNO
TI New approaches for the prevention of **bone metastases** in patients with prostate cancer: A review of preclinical and clinical studies
AU Lassiter L.K.; Carducci M.A.
CS Dr. M.A. Carducci, Division of Medical Oncology, Sidney Kimmel Compreh. C. C. J. H., Cancer Research Building, 1650 Orleans St., Baltimore, MD 21231, United States.
E-mail: carducci@jhmi.edu
SO American Journal of Cancer, (2003), 2/3 (181-199), 197 reference(s)

CODEN: AJCMCB ISSN: 1175-6357
DT Journal; General Review
CY New Zealand
LA English
SL English
AB **Bone metastases** are the most frequent complication of advanced prostate cancer and are responsible for the vast majority of disease-related morbidity and mortality. With the extensive number of predictive models for patients with prostate cancer, we can now determine to some degree which patients are at highest risk for progression to metastatic bone disease and therefore might benefit from earlier or more aggressive therapy. Combining this with our better understanding of the molecular biology underlying the progression to **bone metastasis**, we are able to identify more specific targets or pathways to approach therapeutically to prevent or delay the development of metastatic bone disease. General strategies for the prevention of **bone metastases** include bone-targeting approaches, antimetastatic therapies, and purely antineoplastic agents. Bisphosphonates comprise the most studied and effective of the bone-targeted agents and now have relatively sound clinical data supporting their role not only in the treatment of **bone metastases**, but also in the secondary prevention and, in some cases, primary prevention, of new skeletal complications. Their ease of administration and relatively low short- and long-term toxicities make them ideal for potential treatment earlier in the disease process as well. Radioisotopes have been studied and used for decades for the treatment of painful **bone metastases** but only recently have data accumulated demonstrating their efficacy in the prevention of new metastases. The endothelin receptor antagonist, atrasentan, has recently been shown to delay the progression of systemic disease and potentially improve survival in patients with prostate cancer. It appears to do so, at least in part, by bone-targeting mechanisms. Antimetastatic strategies are also promising for the prevention of **bone metastases** and include matrix metalloproteinase inhibitors, gene therapy, and other novel approaches, such as inhibiting tyrosine kinases or NFκB and immunomodulation of prostate stem cell antigens. Utilizing standard hormonal or cytotoxic therapies in the adjuvant setting has also been studied extensively and in certain groups of patients may provide meaningful clinical benefit in preventing or delaying systemic progression, including **bone metastases**. Finally, as we learn more about molecular synergies with various agents, combinations of these approaches with each other or with more traditional hormonal or chemotherapy agents may be even more effective in the prevention of **bone metastases** in patients with prostate cancer.

L14 ANSWER 8 OF 30 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2004:232354 BIOSIS
DN PREV200400232119
TI Atrasentan delays disease progression in men presenting with metastatic hormone refractory prostate cancer.
AU Schulman, C. [Reprint Author]; Dearnaley, D.; Zonnenberg, B.; Coetzee, L.; Hulting, S.; Isaacson, J.; Allen, A.; Sleep, D.
CS Department of Urology, Hopital Erasme Univ. Clinic Brussels, Brussels, Belgium
SO European Urology Supplements, (February 2004) Vol. 3, No. 2, pp. 157. print.
Meeting Info.: 19th Congress of the European Association of Urology. Vienna, Austria. March 24-27, 2004. European Association of Urology.
ISSN: 1569-9056 (ISSN print).
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English

ED Entered STN: 28 Apr 2004
Last Updated on STN: 28 Apr 2004

L14 ANSWER 9 OF 30 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2003:561996 BIOSIS
DN PREV200300562040
TI Endothelin receptor antagonists in the treatment of prostate cancer.
AU Lassiter, Lance K.; Carducci, Michael A. [Reprint Author]
CS Division of Medical Oncology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 1650 Orleans St, Room 1M-89, Cancer Research Building, Baltimore, MD, 21231, USA
SO Seminars in Oncology, (October 2003) Vol. 30, No. 5, pp. 678-688. print.
ISSN: 0093-7754 (ISSN print).
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 26 Nov 2003
Last Updated on STN: 26 Nov 2003

L14 ANSWER 10 OF 30 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2003:431813 BIOSIS
DN PREV200300431813
TI Gender-specific role of endothelin-1 (ET-1) in pathological bone remodeling.
AU Mohammad, K. S. [Reprint Author]; Yin, J. J. [Reprint Author]; Grubbs, B. G. [Reprint Author]; Cui, Y. [Reprint Author]; Padley, R.; Guise, T. A. [Reprint Author]
CS Molecular Medicine, CTRC, UTHSCSA, IDD, San Antonio, TX, USA
SO Journal of Bone and Mineral Research, (September 2002) Vol. 17, No. Suppl 1, pp. S311. print.
Meeting Info.: Twenty-Fourth Annual Meeting of the American Society for Bone and Mineral Research. San Antonio, Texas, USA. September 20-24, 2002. American Society for Bone and Mineral Research.
ISSN: 0884-0431 (ISSN print).
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 17 Sep 2003
Last Updated on STN: 17 Sep 2003

L14 ANSWER 11 OF 30 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2003:389985 BIOSIS
DN PREV200300389985
TI Treatments for improving survival of patients with prostate cancer.
AU David, Alice K.; Khwaja, Radhika; Hudes, Gary R. [Reprint Author]
CS Department of Medical Oncology, Fox Chase Cancer Center, 7701 Burholme Avenue, Philadelphia, PA, 19111, USA
g_hudes@fccc.edu
SO Drugs & Aging, (2003) Vol. 20, No. 9, pp. 683-699. print.
ISSN: 1170-229X (ISSN print).
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 20 Aug 2003
Last Updated on STN: 18 Sep 2003

L14 ANSWER 12 OF 30 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2003:125326 BIOSIS
DN PREV200300125326
TI Role of endothelin-1 in osteoblastic **bone metastases**.

AU Guise, Theresa A. [Reprint Author]; Yin, Juan Juan; Mohammad, Khalid S.
CS Department of Medicine, Division of Endocrinology and Metabolism, University of Virginia, Aurbach Medical Research Building, PO Box 801419, Charlottesville, VA, 22908, USA
tag4n@virginia.edu
SO Cancer, (February 1 2003) Vol. 97, No. 3 Supplement, pp. 779-784. print.
ISSN: 0008-543X (ISSN print).
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 5 Mar 2003
Last Updated on STN: 5 Mar 2003
AB BACKGROUND: Certain solid tumors metastasize to bone and cause an osteoblastic response. The mechanisms by which tumor cells stimulate this new bone formation are not completely understood. METHODS: The authors identified three breast cancer lines that cause osteoblastic metastases in female nude mice and provided evidence that tumor-produced endothelin-1 (ET-1) mediates the osteoblastic response. RESULTS: Tumor conditioned media, as well as exogenous ET-1, stimulated osteoblast proliferation and new bone formation in cultures of mouse calvariae. These effects were blocked by antagonists of the endothelin A (ETA), but not ETB, receptors. Mice inoculated with the ZR-75-1 breast cancer line and treated with a selective ETA receptor antagonist (ABT-627) had significantly fewer osteoblastic **bone metastases** and less tumor burden compared with untreated mice. In contrast, there was no effect of ABT-627 on osteolytic **bone metastases** caused by ET-1-negative breast cancer, MDA-MB-231. ABT-627 had no effect on growth in vitro or at the orthotopic site of ZR-75-1 or MDA-MB-231 cells. CONCLUSIONS: Collectively, the data suggested that tumor-produced ET-1 mediates osteoblastic **bone metastases** by stimulating osteoblast proliferation and new bone formation. ETA receptor blockade may be useful for prevention and the treatment of osteoblastic **bone metastases** due to breast or prostate cancer.

L14 ANSWER 13 OF 30 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2002:394721 BIOSIS
DN PREV200200394721
TI Endothelin-1 dependent and independent mechanisms concur in the increased bone mass of prostate cancer **bone metastases**.
AU Yang, Jun [Reprint author]; Fizazi, Karim; Peleg, Sara; Sikes, Charles R.; Raymond, Austin K.; Vazquez, Elba S.; Daliani, Danai; Janus, Todd; Logothetis, Christopher J.; Karsenty, Gerard; Navone, Nora M.
CS MD Anderson Cancer Center, Houston, TX, USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2002) Vol. 43, pp. 315. print.
Meeting Info.: 93rd Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA. April 06-10, 2002.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 24 Jul 2002
Last Updated on STN: 24 Jul 2002

L14 ANSWER 14 OF 30 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2002:142771 BIOSIS
DN PREV200200142771
TI Endothelin-1 (ET-1) mediates pathological but not normal bone remodeling.
AU Mohammad, K. S. [Reprint author]; Yin, J. J.; Grubbs, B. G.; Cui, Y.; Padley, R.; Guise, T. A.
CS Medicine/Endocrinology, UTHSCSA, San Antonio, TX, USA
SO Breast Cancer Research and Treatment, (October, 2001) Vol. 69, No. 3, pp.

212. print.
Meeting Info.: 24th Annual San Antonio Breast Cancer Symposium. San Antonio, Texas, USA. December 10-13, 2001.
CODEN: BCTRD6. ISSN: 0167-6806.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 14 Feb 2002
Last Updated on STN: 26 Feb 2002

L14 ANSWER 15 OF 30 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2001:406611 BIOSIS
DN PREV200100406611
TI The effects of endothelin-1 and Abt-627, an endothelin-1 antagonist, in an in vitro model of **bone metastases** from prostate cancer.
AU Fizazi, Karim [Reprint author]; Yang, Jun [Reprint author]; Daliani, Danai [Reprint author]; Logothetis, Christopher [Reprint author]; Peleg, Sara [Reprint author]; Navone, Nora M. [Reprint author]
CS MD Anderson Cancer Center, Houston, TX, USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2001) Vol. 42, pp. 231. print.
Meeting Info.: 92nd Annual Meeting of the American Association for Cancer Research. New Orleans, LA, USA. March 24-28, 2001. American Association for Cancer Research.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 22 Aug 2001
Last Updated on STN: 22 Feb 2002

L14 ANSWER 16 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2004259662 EMBASE
TI Endothelin and the tumorigenic component of bone cancer pain.
AU Peters C.M.; Lindsay T.H.; Pomonis J.D.; Luger N.M.; Ghilardi J.R.; Sevcik M.A.; Mantyh P.W.
CS P.W. Mantyh, Neurosystems Center, 18-208 Moos Tower, University of Minnesota, 515 Delaware Street Southeast, Minneapolis, MN 55455, United States. manty001@umn.edu
SO Neuroscience, (2004) 126/4 (1043-1052).
Refs: 55
ISSN: 0306-4522 CODEN: NRSCDN
PUI S 0306-4522(04)00311-2
CY United Kingdom
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
033 Orthopedic Surgery
037 Drug Literature Index
052 Toxicology
LA English
SL English
AB Tumors including sarcomas and breast, prostate, and lung carcinomas frequently grow in or metastasize to the skeleton where they can induce significant bone remodeling and cancer pain. To define products that are released from tumors that are involved in the generation and maintenance of bone cancer pain, we focus here on endothelin-1 (ET-1) and endothelin receptors as several tumors including human prostate and breast have been shown to express high levels of ETs and the application of ETs to peripheral nerves can induce pain. Here we show that in a murine osteolytic 2472 sarcoma model of bone cancer pain, the 2472 sarcoma cells

express high levels of ET-1, but express low or undetectable levels of endothelin A (ET(A)R) or B (ET(B)R) receptors whereas a subpopulation of sensory neurons express the ET(A)R and non-myelinating Schwann cells express the ET(B)R. Acute (10 mg/kg, i.p.) or chronic (10 mg/kg/day, p.o.) administration of the ET(A)R selective antagonist ABT-627 significantly attenuated ongoing and movement-evoked bone cancer pain and chronic administration of ABT-627 reduced several neurochemical indices of peripheral and central sensitization without influencing tumor growth or bone destruction. In contrast, acute treatment (30 mg/kg, i.p.) with the ET(B)R selective antagonist, A-192621 increased several measures of ongoing and movement evoked pain. As tumor expression and release of ET-1 has been shown to be regulated by the local environment, location specific expression and release of ET-1 by tumor cells may provide insight into the mechanisms that underlie the heterogeneity of bone cancer pain that is frequently observed in humans with multiple skeletal metastases.

L14 ANSWER 17 OF 30 EMBASE
on STN
AN 2004189048 EMBASE
TI PSA relapse prostate cancer: The importance of tailored therapy.
AU Aranha O.; Vaishampayan U.
CS U. Vaishampayan, Department of Internal Medicine, Karmanos Cancer Institute, Wayne State Univ. School of Medicine, Detroit, MI, United States. vaishamu@karmanos.org
SO Urologic Oncology: Seminars and Original Investigations, (2004) 22/1 (62-69).
Refs: 51
ISSN: 1078-1439 CODEN: UOSOAA
PUI S 1078-1439(03)00262-X
CY United States
DT Journal; Conference Article
FS 016 Cancer
028 Urology and Nephrology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Prostate specific antigen (PSA) is an invaluable tumor marker in the detection of early prostate cancer as well as a predictor of recurrence after treatment of localized disease. Current practice entails the use of factors such as pretherapy grade, stage and PSA, PSA doubling time, nature of previous therapy and patient age and functional status for a treatment recommendation. For a PSA relapse post radical prostatectomy, radiation therapy to the prostatic fossa is a primary therapeutic consideration. With careful patient selection, about 30 to 40% of patients are rendered disease free using this approach. For patients with radiation therapy as the primary treatment for their prostate cancer, salvage prostatectomy can be considered, but is rarely feasible. Systemic therapy with hormones is standard if patients are not candidates for the above mentioned salvage local therapies or if they relapse after exhaustive local therapies. Unfortunately androgen suppressive therapy is unlikely to induce cure, or prolonged remissions in PSA relapse prostate cancer. The strategy of addition of chemotherapy or biologic therapy to androgen suppressive therapy is under active investigation. The goal of this therapy is to make an impact on the time to progression to metastatic prostate cancer and correspondingly decrease prostate cancer related mortality. Preliminary results of studies incorporating early chemotherapy in combination with androgen suppressive therapy are encouraging, with improvement in time to progression and overall survival. The evaluation of biologic agents and agents with better toxicity profiles is ongoing. This is very important to make therapy widely applicable and to enable prolonged administration especially in a disease such as prostate cancer with a relatively long

natural history. Strategies of adjuvant and neoadjuvant therapy in locally advanced prostate cancer are exploring the possibility of reducing the chance of PSA relapse by treating micrometastatic disease. This review discusses the current practices in risk stratification and management of PSA relapse prostate cancer. It also highlights the major clinical trials and areas of active investigation in this field. .COPYRGT. 2004 Elsevier Inc. All rights reserved.

L14 ANSWER 18 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2003435088 EMBASE
TI Mechanisms of Osteoblastic Metastases: Role of Endothelin-1.
AU Mohammad K.S.; Guise T.A.
CS Dr. T.A. Guise, University of Virginia, Department of Internal Medicine, Div. of Endocrinology and Metabolism, 450 Ray C. Hunt Drive, Charlottesville, VA 22903, United States. TAG4N@Virginia.edu
SO Clinical Orthopaedics and Related Research, (2003) -/415 SUPPL. (S67-S74). Refs: 67
ISSN: 0009-921X CODEN: CORTBR
CY United States
DT Journal; Conference Article
FS 016 Cancer
029 Clinical Biochemistry
033 Orthopedic Surgery
LA English
SL English
AB Certain solid tumors metastasize to bone, causing an osteoblastic response. The mechanisms by which tumor cells stimulate this new bone formation are not understood completely. We identified three breast cancer lines that cause osteoblastic metastases in female nude mice and provide evidence that tumor-produced endothelin-1 (ET-1) mediates the osteoblastic response. Tumor-conditioned media and exogenous ET-1 stimulated osteoblast proliferation and new bone formation in cultures of calvarias from mice. These effects were blocked by endothelin A (ET(A)) but not by ET(B) receptor antagonists. Mice inoculated with the ZR-75-1 breast cancer line and treated with a selective ET(A) receptor antagonist (ABT-627) had significantly fewer osteoblastic **bone metastases** and less tumor burden compared with untreated mice. In contrast, there was no effect of ABT-627 on osteolytic **bone metastases** caused by ET-1-negative breast cancer, MDA-MB-231. ABT-627 had no effect on cell growth in vitro or at the orthotopic site (mammary fat pad) of ZR-75-1, or MDA-MB-231 cells. Collectively, the data suggest that tumor-produced ET-1 mediates osteoblastic **bone metastases** by stimulating osteoblast proliferation and new bone formation. Endothelin A receptor blockade may be useful for the prevention and treatment of osteoblastic **bone metastases** attributable to breast or prostate cancer.

L14 ANSWER 19 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2003426429 EMBASE
TI Endothelin Receptor Antagonists in the Treatment of Prostate Cancer.
AU Lassiter L.K.; Carducci M.A.
CS Dr. M.A. Carducci, Division of Medical Oncology, Cancer Research Building, Sidney Kimmel Compreh. Cancer Center, 1650 Orleans St, Baltimore, MD 21231, United States
SO Seminars in Oncology, (2003) 30/5 (678-688). Refs: 72
ISSN: 0093-7754 CODEN: SOLGAV
CY United States
DT Journal; General Review
FS 016 Cancer
028 Urology and Nephrology
030 Pharmacology

037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB The endothelin (ET) axis represents a novel and exciting target in the treatment of prostate cancer. ET-1, acting primarily through the endothelin A receptor (ET(A)), is integrally involved in multiple facets of prostate cancer progression, including cell growth, inhibition of apoptosis, angiogenesis, development and progression of **bone metastases**, and mediation of pain responses. Clinical trials with the ET(A) antagonist, atrasentan, have demonstrated good tolerability, with the most common adverse events being headache, rhinitis, and peripheral edema. These trials have demonstrated statistically significant improvements in pain measures, prostate-specific antigen (PSA) kinetics, biologic markers of bone changes, and development of **bone metastases**. There have also been consistent improvements in time to progression, although not always statistically significant. Ongoing studies in a variety of patient populations will better define the role of ET receptor antagonists in the treatment of men with prostate cancer. In this article, we review the biology and pathophysiology of the ET axis in prostate cancer, critically analyze the major clinical trials reported to date, and discuss some emerging data and how it may impact the way we proceed in the future with the development of this class of drugs in prostate cancer.

L14 ANSWER 20 OF 30 EMBASE
on STN
AN 2003402002 EMBASE
TI Skeletal complications of malignancy - Third North American Symposium: 25-27 April 2002, Bethesda, MD, USA.
AU Bagi C.
CS C. Bagi, Pfizer Inc., Groton Laboratories, Eastern Point Road 8118E/3, Groton, CT 06340, United States. cedo_bagi@groton.pfizer.com
SO IDrugs, (2002) 5/6 (553-556).
ISSN: 1369-7056 CODEN: IDRUFN
CY United Kingdom
DT Journal; Conference Article
FS 016 Cancer
017 Public Health, Social Medicine and Epidemiology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
014 Radiology
LA English
SL English
AB Interest in the skeletal complications of malignancy continues to increase rapidly. There are several reasons for this growing trend including an aging population and higher incidence of cancer, improved diagnostic tools, and effective anticancer therapy. In addition, life expectancy is prolonged, in particular those patients suffering from breast and prostate cancer. **Bone metastases** are a frequent event in a variety of cancer types. Dissemination of the carcinomas of the breast and prostate to the skeleton is particularly prevalent and also a notable feature of malignancy originating in the lungs, thyroid and kidneys. Multiple myeloma is a unique neoplastic disorder associated with extensive bone involvement. Important clinical problems that arise from cancer metastases to bone include humoral hypercalcemia of malignancy, cancer-associated osteoporosis and significant implications on the quality of life of cancer patients including bone pain. The major topic of the conference was treatment modalities targeting the prevention of skeletal disease. One particular focus was given to stromal-derived cytokines and growth factors due to evidence which indicates the critical role that bone marrow and stroma play in homing of tumors to the bone and development of

bone metastases. .COPYRGT. PharmaPress Ltd.

L14 ANSWER 21 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2003379832 EMBASE
TI A causal role for endothelin-1 in the pathogenesis of osteoblastic **bone metastases**.
AU Yin J.J.; Mohammad K.S.; Kakonen S.M.; Harris S.; Wu-Wong J.R.; Wessale J.L.; Padley R.J.; Garrett I.R.; Chirgwin J.M.; Guise T.A.
CS T.A. Guise, Department of Internal Medicine, Division of Endocrinology, University of Virginia, P.O. Box 801419, Charlottesville, VA 22908, United States. tag4n@virginia.edu
SO Proceedings of the National Academy of Sciences of the United States of America, (16 Sep 2003) 100/19 (10954-10959).
Refs: 42
ISSN: 0027-8424 CODEN: PNASA6
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
016 Cancer
037 Drug Literature Index
LA English
SL English
AB Osteoblastic **bone metastases** are common in prostate and breast cancer patients, but mechanisms by which tumor cells stimulate new bone formation are unclear. We identified three breast cancer cell lines that cause osteoblastic metastases in a mouse model and secrete endothelin-1. Tumor-produced endothelin-1 stimulates new bone formation in vitro and osteoblastic metastases in vivo via the endothelin A receptor. Treatment with an orally active endothelin A receptor antagonist dramatically decreased **bone metastases** and tumor burden in mice inoculated with ZR-75-1 cells. Tumor-produced endothelin-1 may have a major role in the establishment of osteoblastic **bone metastases**, and endothelin A receptor blockade represents effective treatment.

L14 ANSWER 22 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2003296046 EMBASE
TI New approaches for the prevention of **bone metastases** in patients with prostate cancer: A review of preclinical and clinical studies.
AU Lassiter L.K.; Carducci M.A.
CS Dr. M.A. Carducci, Division of Medical Oncology, Sidney Kimmel Compreh. C. C. J. H., Cancer Research Building, 1650 Orleans St., Baltimore, MD 21231, United States. carducci@jhmi.edu
SO American Journal of Cancer, (2003) 2/3 (181-199).
Refs: 197
ISSN: 1175-6357 CODEN: AJCMCB
CY New Zealand
DT Journal; General Review
FS 016 Cancer
028 Urology and Nephrology
033 Orthopedic Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB **Bone metastases** are the most frequent complication of advanced prostate cancer and are responsible for the vast majority of disease-related morbidity and mortality. With the extensive number of predictive models for patients with prostate cancer, we can now determine to some degree which patients are at highest risk for progression to metastatic bone disease and therefore might benefit from earlier or more

aggressive therapy. Combining this with our better understanding of the molecular biology underlying the progression to **bone metastasis**, we are able to identify more specific targets or pathways to approach therapeutically to prevent or delay the development of metastatic bone disease. General strategies for the prevention of **bone metastases** include bone-targeting approaches, antimetastatic therapies, and purely antineoplastic agents. Bisphosphonates comprise the most studied and effective of the bone-targeted agents and now have relatively sound clinical data supporting their role not only in the treatment of **bone metastases**, but also in the secondary prevention and, in some cases, primary prevention, of new skeletal complications. Their ease of administration and relatively low short- and long-term toxicities make them ideal for potential treatment earlier in the disease process as well. Radioisotopes have been studied and used for decades for the treatment of painful **bone metastases** but only recently have data accumulated demonstrating their efficacy in the prevention of new metastases. The endothelin receptor antagonist, atrasentan, has recently been shown to delay the progression of systemic disease and potentially improve survival in patients with prostate cancer. It appears to do so, at least in part, by bone-targeting mechanisms. Antimetastatic strategies are also promising for the prevention of **bone metastases** and include matrix metalloproteinase inhibitors, gene therapy, and other novel approaches, such as inhibiting tyrosine kinases or NFκB and immunomodulation of prostate stem cell antigens. Utilizing standard hormonal or cytotoxic therapies in the adjuvant setting has also been studied extensively and in certain groups of patients may provide meaningful clinical benefit in preventing or delaying systemic progression, including **bone metastases**. Finally, as we learn more about molecular synergies with various agents, combinations of these approaches with each other or with more traditional hormonal or chemotherapy agents may be even more effective in the prevention of **bone metastases** in patients with prostate cancer.

L14 ANSWER 23 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2003126896 EMBASE
TI The role of endothelin in hormone-refractory prostate cancer.
AU Zonnenberg B.A.; Voest E.E.
CS E.E. Voest, Department of Medicinal Oncology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, Netherlands. e.e.voest@azu.nl
SO European Urology, Supplement, (2003) 2/3 (9-14).
Refs: 43
ISSN: 1569-9056 CODEN: EUSUAU
CY Netherlands
DT Journal; General Review
FS 005 General Pathology and Pathological Anatomy
016 Cancer
028 Urology and Nephrology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Aggressive chemotherapy has made only a limited contribution to improvements in patient prognosis and well-being in hormone-refractory prostate cancer (HRPC). Such poor progress results from the biological basis of the disease, localisation of the tumour and the relatively high age of affected men, and leaves patients with a dismal prognosis. Given the palliative role of current treatments, attention has focused on the development of therapies targeted at non-androgenic mediators of prostate growth. Endothelin-1 (ET-1), a 21-amino-acid peptide produced by endothelial cells and prevalent in seminal fluid, has been identified as one such mediator. In addition to its potent mitogenic and

vasoconstrictive properties, ET-1 has been shown to suppress apoptosis and induce angiogenesis. In HRPC cells, increased levels of ET-1 have been observed. ET-1 mediates its effects through two receptors, of which the endothelin-A (ET(A)) receptor is most important in prostate cancer. An up-regulation of ET(A) receptor levels and decreased expression of endothelin-B (ET(B)) receptors is observed in HRPC cells. Taken together, these factors are thought to play a significant role in the progression of the disease. Research has, therefore, focused on development of ET-1 antagonists to disrupt the mitogenic and angiogenic effects of ET-1 and slow disease progression. As ET-1 is also an important factor in the development of new bone, ET-1 antagonists may potentially inhibit the development of skeletal metastases and associated pain, which characterise this disease. Atrasentan, a highly specific ET(A) receptor antagonist, is currently in clinical development. Data are awaited from clinical trials to confirm the role of this agent in the treatment of HRPC.

L14 ANSWER 24 OF 30 EMBASE
on STN
AN 2001272389 EMBASE
TI News from the 37th annual meeting of the American society of clinical oncologists.
AU Wapner J.
SO Oncology Spectrums, (2001) 2/6 (378-379).
ISSN: 1532-8554 CODEN: OENCAH
CY United States
DT Journal; Article
FS 016 Cancer
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LA English

L14 ANSWER 25 OF 30 EMBASE
on STN
AN 2001229203 EMBASE
TI New drugs slow progression of prostate cancer.
SO European Journal of Cancer, (2001) 37/11 (1325).
ISSN: 0959-8049 CODEN: EJCAEL
PUI S 0959-8049(01)00194-0
CY United Kingdom
DT Journal; Note
FS 016 Cancer
037 Drug Literature Index
LA English

L14 ANSWER 26 OF 30 TOXCENTER
AN 2003:290353 TOXCENTER
CP
DN CA13926390556G
TI Endothelin receptor antagonists in the treatment of prostate cancer
AU Lassiter, Lance K.; Carducci, Michael A.
CS Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, 21231, USA.
SO Seminars in Oncology, (2003) Vol. 30, No. 5, pp. 678-688.
CODEN: SOLGAV. ISSN: 0093-7754.
CY UNITED STATES
DT Journal
FS CAPLUS
OS CAPLUS 2003:925734
LA English
ED Entered STN: 20031216
Last Updated on STN: 20031223
AB A review. The endothelin (ET) axis represents a novel and exciting target

in the treatment of prostate cancer. ET-1, acting primarily through the endothelin A receptor (ETA), is integrally involved in multiple facets of prostate cancer progression, including cell growth, inhibition of apoptosis, angiogenesis, development and progression of **bone metastases**, and mediation of pain responses. Clin. trials with the ETA antagonist, atrasentan, have demonstrated good tolerability, with the most common adverse events being headache, rhinitis, and peripheral edema. These trials have demonstrated statistically significant improvements in pain measures, prostate-specific antigen (PSA) kinetics, biol. markers of bone changes, and development of **bone metastases**. There have also been consistent improvements in time to progression, although not always statistically significant. Ongoing studies in a variety of patient populations will better define the role of ET receptor antagonists in the treatment of men with prostate cancer. In this article, we review the biol. and pathophysiol. of the ET axis in prostate cancer, critically analyze the major clin. trials reported to date, and discuss some emerging data and how it may impact the way we proceed in the future with the development of this class of drugs in prostate cancer.

L14 ANSWER 27 OF 30 TOXCENTER COPYRIGHT 2004 ACS on STN
AN 2003:282510 TOXCENTER
CP Copyright 2004 BIOSIS
DN PREV200300562040
TI Endothelin receptor antagonists in the treatment of prostate cancer
AU Lassiter, Lance K.; Carducci, Michael A. [Reprint Author]
CS Division of Medical Oncology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 1650 Orleans St, Room 1M-89, Cancer Research Building, Baltimore, MD, 21231, USA
SO Seminars in Oncology, (October 2003) Vol. 30, No. 5, pp. 678-688. print. ISSN: 0093-7754 (ISSN print).
DT Article
General Review; (Literature Review)
FS BIOSIS
OS BIOSIS 2003:561996
LA English
ED Entered STN: 20031202
Last Updated on STN: 20031202

L14 ANSWER 28 OF 30 TOXCENTER COPYRIGHT 2004 ACS on STN
AN 2003:247216 TOXCENTER
CP Copyright 2004 ACS
DN CA13918270402G
TI Suppression of Prostate Cancer Induced Bone Remodeling by The Endothelin Receptor A Antagonist Atrasentan
AU Nelson, Joel B.; Nabulsi, Azmi A.; Vogelzang, Nicholas J.; Breul, Jurgen; Zonnenberg, Bernard A.; Daliani, Danai D.; Schulman, Claude C.; Carducci, Michael A.
CS Sidney Kimmel Comprehensive Cancer Cent., The Johns Hopkins Univ. Sch. Med., Baltimore, MD, USA.
SO Journal of Urology (Hagerstown, MD, United States), (2003) Vol. 169, No. 3, pp. 1143-1149.
CODEN: JOURAA. ISSN: 0022-5347.
CY UNITED STATES
DT Journal
FS CAPLUS
OS CAPLUS 2003:124519
LA English
ED Entered STN: 20031014
Last Updated on STN: 20031028
AB We examined the effects of atrasentan (endothelin-A receptor antagonist) on bone deposition and resorption markers and on bone scan index. This double-blind, randomized, placebo controlled clin. trial of hormone refractory prostate cancer patients was done at 74 medical centers in the

United States and Europe. A total of 288 asymptomatic patients with hormone refractory prostate adenocarcinoma and evidence of metastatic disease were randomized to 1 of 3 treatment groups, namely 2.5 mg. atrasentan, 10 mg. atrasentan or placebo administered orally daily until disease progression. The main outcomes measures were changes in bone deposition markers (total alkaline phosphatase and bone alkaline phosphatase) and bone resorption (N-telopeptides, C-telopeptides and deoxypyridinoline), and in the bone scan index. At baseline markers of bone deposition and resorption were elevated 1.4 to 2.7-fold above resp. upper limits of normal. Subjects receiving placebo experienced a 58% elevation in mean total alkaline phosphatase and a 99% elevation in mean bone alkaline phosphatase (p <0.001), whereas subjects receiving 10 mg. atrasentan maintained stable mean total alkaline phosphatase and bone alkaline phosphatase values compared with baseline. N-telopeptides, C-telopeptides and deoxypyridinoline elevation from baseline were consistently less in patients receiving 10 mg. atrasentan compared with placebo. Similar trends were observed in subjects who received 2.5 mg. atrasentan. Changes in clin. bone scan studies paralleled bone marker changes. Atrasentan suppressed markers of biochem. and **bone metastasis** and demonstrates clin. activity for hormone refractory prostate cancer.

L14 ANSWER 29 OF 30 TOXCENTER COPYRIGHT 2004 ACS on STN
AN 2002:120290 TOXCENTER
CP Copyright 2004 ACS
DN CA13623350550G
TI Methods of treating cancer and the pain associated therewith using endothelin antagonists
AU Janus, Todd J.; Padley, Robert J.
PI US 2002055457 A1 9 May 2002
SO (2002) U.S. Pat. Appl. Publ., 24 pp.
CODEN: USXXCO.
CY UNITED STATES
DT Patent
FS CAPLUS
OS CAPLUS 2002:354070
LA English
ED Entered STN: 20020528
Last Updated on STN: 20030624
AB The instant invention is directed to methods for the inhibition of **bone metastases**, methods for the prevention of growth of new metastases, methods for the inhibition of bone turnover, and methods for the prevention of bone loss in patients, including cancer patients, using an endothelin ET-A receptor antagonist.

L14 ANSWER 30 OF 30 TOXCENTER COPYRIGHT 2004 ACS on STN
AN 2002:57459 TOXCENTER
CP Copyright 2004 ACS
DN CA13611161346J
TI Methods of treating cancer and the pain associated therewith using endothelin antagonists
AU Janus, Todd J.; Padley, Robert J.
CS ASSIGNEE: Abbott Laboratories
PI WO 2002011713 A2 14 Feb 2002
SO (2002) PCT Int. Appl., 86 pp.
CODEN: PIXXD2.
CY UNITED STATES
DT Patent
FS CAPLUS
OS CAPLUS 2002:122776
LA English
ED Entered STN: 20020305

Last Updated on STN: 20030624

AB The instant invention is directed to methods for the inhibition of **bone metastases**, methods for the prevention of growth of new metastases, methods for the inhibition of bone turnover, and methods for the prevention of bone loss in patients, including cancer patients, using an endothelin ET-A receptor antagonist.

=> d l15 1-9 bib abs
YOU HAVE REQUESTED DATA FROM FILE 'CAPLUS, USPATFULL, BIOTECHNO, BIOSIS, EMBASE' - CONTINUE? (Y)/N:y

L15 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:354796 CAPLUS
DN 140:368653
TI Endothelin receptor antagonist-EGF receptor tyrosine kinase inhibitor combination for the treatment of cancer
IN Boyle, Francis Thomas; Curwen, Jon Owen; Gallagher, Neil James; Hancox, Ursula Joy; Hughes, Andrew Mark; Johnstone, Donna; Taylor, Sian Tomiko; Tonge, David William
PA Astrazeneca AB, Swed.; Astrazeneca UK Limited
SO PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004035057	A1	20040429	WO 2003-GB4347	20031007

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI GB 2002-23854 A 20021012

AB A combination, comprising an endothelin receptor antagonist (e.g. ZD4054), or a pharmaceutically acceptable salt thereof, and an EGF receptor tyrosine kinase inhibitor (e.g. ZD1839), or a pharmaceutically acceptable salt thereof, is described. The combination of the invention is useful for the treatment of cancer, e.g. prostate cancer.
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 9 USPATFULL on STN
AN 2002:106248 USPATFULL
TI Methods of treating cancer and the pain associated therewith using endothelin antagonists
IN Janus, Todd J., Gurnee, IL, UNITED STATES
Padley, Robert J., Lake Bluff, IL, UNITED STATES
PI US 2002055457 A1 20020509
AI US 2001-923616 A1 20010806 (9)
PRAI US 2000-223486P 20000807 (60)
DT Utility
FS APPLICATION
LREP Steven F. Weinstock, Abbott Laboratories, D-377/AP6D, 100 Abbott Park Road, Abbott Park, IL, 60064-6050

CLMN Number of Claims: 58
ECL Exemplary Claim: 1
DRWN 7 Drawing Page(s)
LN.CNT 1394
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The instant invention is directed to methods for the inhibition of bone metastases, methods for the prevention of growth of new metastases, methods for the inhibition of bone turnover, and methods for the prevention of bone loss in patients, including cancer patients, using an endothelin ET-A receptor antagonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 3 OF 9 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN
AN 2003:37140134 BIOTECHNO
TI A causal role for endothelin-1 in the pathogenesis of **osteoblastic** bone metastases
AU Yin J.J.; Mohammad K.S.; Kakonen S.M.; Harris S.; Wu-Wong J.R.; Wessale J.L.; Padley R.J.; Garrett I.R.; Chirgwin J.M.; Guise T.A.
CS T.A. Guise, Department of Internal Medicine, Division of Endocrinology, University of Virginia, P.O. Box 801419, Charlottesville, VA 22908, United States.
E-mail: tag4n@virginia.edu
SO Proceedings of the National Academy of Sciences of the United States of America, (16 SEP 2003), 100/19 (10954-10959), 42 reference(s)
CODEN: PNASA6 ISSN: 0027-8424
DT Journal; Article
CY United States
LA English
SL English
AB **Osteoblastic** bone metastases are common in prostate and breast cancer patients, but mechanisms by which tumor cells stimulate new bone formation are unclear. We identified three breast cancer cell lines that cause **osteoblastic** metastases in a mouse model and secrete endothelin-1. Tumor-produced endothelin-1 stimulates new bone formation in vitro and **osteoblastic** metastases in vivo via the endothelin A receptor. Treatment with an orally active endothelin A receptor antagonist dramatically decreased bone metastases and tumor burden in mice inoculated with ZR-75-1 cells. Tumor-produced endothelin-1 may have a major role in the establishment of **osteoblastic** bone metastases, and endothelin A receptor blockade represents effective treatment.

L15 ANSWER 4 OF 9 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2003:125326 BIOSIS
DN PREV200300125326
TI Role of endothelin-1 in **osteoblastic** bone metastases.
AU Guise, Theresa A. [Reprint Author]; Yin, Juan Juan; Mohammad, Khalid S.
CS Department of Medicine, Division of Endocrinology and Metabolism, University of Virginia, Aurbach Medical Research Building, PO Box 801419, Charlottesville, VA, 22908, USA
tag4n@virginia.edu
SO Cancer, (February 1 2003) Vol. 97, No. 3 Supplement, pp. 779-784. print.
ISSN: 0008-543X (ISSN print).
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 5 Mar 2003
Last Updated on STN: 5 Mar 2003
AB BACKGROUND: Certain solid tumors metastasize to bone and cause an **osteoblastic** response. The mechanisms by which tumor cells stimulate this new bone formation are not completely understood. METHODS: The authors identified three breast cancer lines that cause **osteoblastic** metastases in female nude mice and provided evidence

that tumor-produced endothelin-1 (ET-1) mediates the **osteoblastic** response. RESULTS: Tumor conditioned media, as well as exogenous ET-1, stimulated **osteoblast** proliferation and new bone formation in cultures of mouse calvariae. These effects were blocked by antagonists of the endothelin A (ETA), but not ETB, receptors. Mice inoculated with the ZR-75-1 breast cancer line and treated with a selective ETA receptor antagonist (ABT-627) had significantly fewer **osteoblastic** bone metastases and less tumor burden compared with untreated mice. In contrast, there was no effect of ABT-627 on osteolytic bone metastases caused by ET-1-negative breast cancer, MDA-MB-231. ABT-627 had no effect on growth in vitro or at the orthotopic site of ZR-75-1 or MDA-MB-231 cells. CONCLUSIONS: Collectively, the data suggested that tumor-produced ET-1 mediates **osteoblastic** bone metastases by stimulating **osteoblast** proliferation and new bone formation. ETA receptor blockade may be useful for prevention and the treatment of **osteoblastic** bone metastases due to breast or prostate cancer.

L15 ANSWER 5 OF 9 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2002:394721 BIOSIS
DN PREV200200394721
TI Endothelin-1 dependent and independent mechanisms concur in the increased bone mass of prostate cancer bone metastases.
AU Yang, Jun [Reprint author]; Fizazi, Karim; Peleg, Sara; Sikes, Charles R.; Raymond, Austin K.; Vazquez, Elba S.; Daliani, Danai; Janus, Todd; Logothetis, Christopher J.; Karsenty, Gerard; Navone, Nora M.
CS MD Anderson Cancer Center, Houston, TX, USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2002) Vol. 43, pp. 315. print.
Meeting Info.: 93rd Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA. April 06-10, 2002.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 24 Jul 2002
Last Updated on STN: 24 Jul 2002

L15 ANSWER 6 OF 9 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2002:142771 BIOSIS
DN PREV200200142771
TI Endothelin-1 (ET-1) mediates pathological but not normal bone remodeling.
AU Mohammad, K. S. [Reprint author]; Yin, J. J.; Grubbs, B. G.; Cui, Y.; Padley, R.; Guise, T. A.
CS Medicine/Endocrinology, UTHSCSA, San Antonio, TX, USA
SO Breast Cancer Research and Treatment, (October, 2001) Vol. 69, No. 3, pp. 212. print.
Meeting Info.: 24th Annual San Antonio Breast Cancer Symposium. San Antonio, Texas, USA. December 10-13, 2001.
CODEN: BCTRD6. ISSN: 0167-6806.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 14 Feb 2002
Last Updated on STN: 26 Feb 2002

L15 ANSWER 7 OF 9 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2001:406611 BIOSIS
DN PREV200100406611
TI The effects of endothelin-1 and Abt-627, an endothelin-1 antagonist, in an in vitro model of bone metastases from prostate cancer.
AU Fizazi, Karim [Reprint author]; Yang, Jun [Reprint author]; Daliani, Danai [Reprint author]; Logothetis, Christopher [Reprint author]; Peleg, Sara [Reprint author]; Navone, Nora M. [Reprint author]
CS MD Anderson Cancer Center, Houston, TX, USA

SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2001) Vol. 42, pp. 231. print.
Meeting Info.: 92nd Annual Meeting of the American Association for Cancer Research. New Orleans, LA, USA. March 24-28, 2001. American Association for Cancer Research.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 22 Aug 2001
Last Updated on STN: 22 Feb 2002

L15 ANSWER 8 OF 9 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2003435088 EMBASE
TI Mechanisms of **Osteoblastic** Metastases: Role of Endothelin-1.
AU Mohammad K.S.; Guise T.A.
CS Dr. T.A. Guise, University of Virginia, Department of Internal Medicine, Div. of Endocrinology and Metabolism, 450 Ray C. Hunt Drive, Charlottesville, VA 22903, United States. TAG4N@Virginia.edu
SO Clinical Orthopaedics and Related Research, (2003) -/415 SUPPL. (S67-S74). Refs: 67
ISSN: 0009-921X CODEN: CORTBR
CY United States
DT Journal; Conference Article
FS 016 Cancer
029 Clinical Biochemistry
033 Orthopedic Surgery
LA English
SL English
AB Certain solid tumors metastasize to bone, causing an **osteoblastic** response. The mechanisms by which tumor cells stimulate this new bone formation are not understood completely. We identified three breast cancer lines that cause **osteoblastic** metastases in female nude mice and provide evidence that tumor-produced endothelin-1 (ET-1) mediates the **osteoblastic** response. Tumor-conditioned media and exogenous ET-1 stimulated **osteoblast** proliferation and new bone formation in cultures of calvarias from mice. These effects were blocked by endothelin A (ET(A)) but not by ET(B) receptor antagonists. Mice inoculated with the ZR-75-1 breast cancer line and treated with a selective ET(A) receptor antagonist (ABT-627) had significantly fewer **osteoblastic** bone metastases and less tumor burden compared with untreated mice. In contrast, there was no effect of ABT-627 on osteolytic bone metastases caused by ET-1-negative breast cancer, MDA-MB-231. ABT-627 had no effect on cell growth in vitro or at the orthotopic site (mammary fat pad) of ZR-75-1, or MDA-MB-231 cells. Collectively, the data suggest that tumor-produced ET-1 mediates **osteoblastic** bone metastases by stimulating **osteoblast** proliferation and new bone formation. Endothelin A receptor blockade may be useful for the prevention and treatment of **osteoblastic** bone metastases attributable to breast or prostate cancer.

L15 ANSWER 9 OF 9 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2003379832 EMBASE
TI A causal role for endothelin-1 in the pathogenesis of **osteoblastic** bone metastases.
AU Yin J.J.; Mohammad K.S.; Kakonen S.M.; Harris S.; Wu-Wong J.R.; Wessale J.L.; Padley R.J.; Garrett I.R.; Chirgwin J.M.; Guise T.A.
CS T.A. Guise, Department of Internal Medicine, Division of Endocrinology, University of Virginia, P.O. Box 801419, Charlottesville, VA 22908, United States. tag4n@virginia.edu
SO Proceedings of the National Academy of Sciences of the United States of America, (16 Sep 2003) 100/19 (10954-10959).

Refs: 42
ISSN: 0027-8424 CODEN: PNASA6
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
016 Cancer
037 Drug Literature Index
LA English
SL English
AB **Osteoblastic** bone metastases are common in prostate and breast cancer patients, but mechanisms by which tumor cells stimulate new bone formation are unclear. We identified three breast cancer cell lines that cause **osteoblastic** metastases in a mouse model and secrete endothelin-1. Tumor-produced endothelin-1 stimulates new bone formation in vitro and **osteoblastic** metastases in vivo via the endothelin A receptor. Treatment with an orally active endothelin A receptor antagonist dramatically decreased bone metastases and tumor burden in mice inoculated with ZR-75-1 cells. Tumor-produced endothelin-1 may have a major role in the establishment of **osteoblastic** bone metastases, and endothelin A receptor blockade represents effective treatment.

=> d l16 1-8 bib abs
YOU HAVE REQUESTED DATA FROM FILE 'USPATFULL, BIOTECHNO, BIOSIS, EMBASE' -
CONTINUE? (Y)/N:y

L16 ANSWER 1 OF 8 USPATFULL on STN
AN 2002:106248 USPATFULL
TI Methods of treating cancer and the pain associated therewith using endothelin antagonists
IN Janus, Todd J., Gurnee, IL, UNITED STATES
Padley, Robert J., Lake Bluff, IL, UNITED STATES
PI US 2002055457 A1 20020509
AI US 2001-923616 A1 20010806 (9)
PRAI US 2000-223486P 20000807 (60)
DT Utility
FS APPLICATION
LREP Steven F. Weinstock, Abbott Laboratories, D-377/AP6D, 100 Abbott Park Road, Abbott Park, IL, 60064-6050
CLMN Number of Claims: 58
ECL Exemplary Claim: 1
DRWN 7 Drawing Page(s)
LN.CNT 1394
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The instant invention is directed to methods for the inhibition of **bone metastases**, methods for the prevention of growth of new metastases, methods for the inhibition of bone turnover, and methods for the prevention of bone loss in patients, including cancer patients, using an endothelin ET-A receptor antagonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 2 OF 8 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN
AN 2003:37140134 BIOTECHNO
TI A causal role for endothelin-1 in the pathogenesis of **osteoblastic bone metastases**
AU Yin J.J.; Mohammad K.S.; Kakonen S.M.; Harris S.; Wu-Wong J.R.; Wessale J.L.; Padley R.J.; Garrett I.R.; Chirgwin J.M.; Guise T.A.
CS T.A. Guise, Department of Internal Medicine, Division of Endocrinology, University of Virginia, P.O. Box 801419, Charlottesville, VA 22908, United States.
E-mail: tag4n@virginia.edu

SO Proceedings of the National Academy of Sciences of the United States of America, (16 SEP 2003), 100/19 (10954-10959), 42 reference(s)
CODEN: PNASA6 ISSN: 0027-8424
DT Journal; Article
CY United States
LA English
SL English
AB **Osteoblastic bone metastases** are common in prostate and breast cancer patients, but mechanisms by which tumor cells stimulate new bone formation are unclear. We identified three breast cancer cell lines that cause **osteoblastic** metastases in a mouse model and secrete endothelin-1. Tumor-produced endothelin-1 stimulates new bone formation in vitro and **osteoblastic** metastases in vivo via the endothelin A receptor. Treatment with an orally active endothelin A receptor antagonist dramatically decreased **bone metastases** and tumor burden in mice inoculated with ZR-75-1 cells. Tumor-produced endothelin-1 may have a major role in the establishment of **osteoblastic bone metastases**, and endothelin A receptor blockade represents effective treatment.

L16 ANSWER 3 OF 8 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2003:125326 BIOSIS
DN PREV200300125326
TI Role of endothelin-1 in **osteoblastic bone metastases**.
AU Guise, Theresa A. [Reprint Author]; Yin, Juan Juan; Mohammad, Khalid S.
CS Department of Medicine, Division of Endocrinology and Metabolism, University of Virginia, Aurbach Medical Research Building, PO Box 801419, Charlottesville, VA, 22908, USA
tag4n@virginia.edu
SO Cancer, (February 1 2003) Vol. 97, No. 3 Supplement, pp. 779-784. print.
ISSN: 0008-543X (ISSN print).
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 5 Mar 2003
Last Updated on STN: 5 Mar 2003
AB BACKGROUND: Certain solid tumors metastasize to bone and cause an **osteoblastic** response. The mechanisms by which tumor cells stimulate this new bone formation are not completely understood. METHODS: The authors identified three breast cancer lines that cause **osteoblastic** metastases in female nude mice and provided evidence that tumor-produced endothelin-1 (ET-1) mediates the **osteoblastic** response. RESULTS: Tumor conditioned media, as well as exogenous ET-1, stimulated **osteoblast** proliferation and new bone formation in cultures of mouse calvariae. These effects were blocked by antagonists of the endothelin A (ETA), but not ETB, receptors. Mice inoculated with the ZR-75-1 breast cancer line and treated with a selective ETA receptor antagonist (ABT-627) had significantly fewer **osteoblastic bone metastases** and less tumor burden compared with untreated mice. In contrast, there was no effect of ABT-627 on osteolytic **bone metastases** caused by ET-1-negative breast cancer, MDA-MB-231. ABT-627 had no effect on growth in vitro or at the orthotopic site of ZR-75-1 or MDA-MB-231 cells. CONCLUSIONS: Collectively, the data suggested that tumor-produced ET-1 mediates **osteoblastic bone metastases** by stimulating **osteoblast** proliferation and new bone formation. ETA receptor blockade may be useful for prevention and the treatment of **osteoblastic bone metastases** due to breast or prostate cancer.

L16 ANSWER 4 OF 8 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2002:394721 BIOSIS
DN PREV200200394721
TI Endothelin-1 dependent and independent mechanisms concur in the increased

bone mass of prostate cancer **bone metastases**.
AU Yang, Jun [Reprint author]; Fizazi, Karim; Peleg, Sara; Sikes, Charles R.; Raymond, Austin K.; Vazquez, Elba S.; Daliani, Danai; Janus, Todd; Logothetis, Christopher J.; Karsenty, Gerard; Navone, Nora M.
CS MD Anderson Cancer Center, Houston, TX, USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2002) Vol. 43, pp. 315. print.
Meeting Info.: 93rd Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA. April 06-10, 2002.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 24 Jul 2002
Last Updated on STN: 24 Jul 2002

L16 ANSWER 5 OF 8 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2002:142771 BIOSIS
DN PREV200200142771
TI Endothelin-1 (ET-1) mediates pathological but not normal bone remodeling.
AU Mohammad, K. S. [Reprint author]; Yin, J. J.; Grubbs, B. G.; Cui, Y.; Padley, R.; Guise, T. A.
CS Medicine/Endocrinology, UTHSCSA, San Antonio, TX, USA
SO Breast Cancer Research and Treatment, (October, 2001) Vol. 69, No. 3, pp. 212. print.
Meeting Info.: 24th Annual San Antonio Breast Cancer Symposium. San Antonio, Texas, USA. December 10-13, 2001.
CODEN: BCTRD6. ISSN: 0167-6806.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 14 Feb 2002
Last Updated on STN: 26 Feb 2002

L16 ANSWER 6 OF 8 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2001:406611 BIOSIS
DN PREV200100406611
TI The effects of endothelin-1 and Abt-627, an endothelin-1 antagonist, in an in vitro model of **bone metastases** from prostate cancer.
AU Fizazi, Karim [Reprint author]; Yang, Jun [Reprint author]; Daliani, Danai [Reprint author]; Logothetis, Christopher [Reprint author]; Peleg, Sara [Reprint author]; Navone, Nora M. [Reprint author]
CS MD Anderson Cancer Center, Houston, TX, USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2001) Vol. 42, pp. 231. print.
Meeting Info.: 92nd Annual Meeting of the American Association for Cancer Research. New Orleans, LA, USA. March 24-28, 2001. American Association for Cancer Research.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 22 Aug 2001
Last Updated on STN: 22 Feb 2002

L16 ANSWER 7 OF 8 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2003435088 EMBASE
TI Mechanisms of **Osteoblastic** Metastases: Role of Endothelin-1.
AU Mohammad K.S.; Guise T.A.
CS Dr. T.A. Guise, University of Virginia, Department of Internal Medicine, Div. of Endocrinology and Metabolism, 450 Ray C. Hunt Drive, Charlottesville, VA 22903, United States. TAG4N@Virginia.edu

SO Clinical Orthopaedics and Related Research, (2003) -/415 SUPPL. (S67-S74).
Refs: 67
ISSN: 0009-921X CODEN: CORTBR
CY United States
DT Journal; Conference Article
FS 016 Cancer
029 Clinical Biochemistry
033 Orthopedic Surgery
LA English
SL English
AB Certain solid tumors metastasize to bone, causing an **osteoblastic** response. The mechanisms by which tumor cells stimulate this new bone formation are not understood completely. We identified three breast cancer lines that cause **osteoblastic** metastases in female nude mice and provide evidence that tumor-produced endothelin-1 (ET-1) mediates the **osteoblastic** response. Tumor-conditioned media and exogenous ET-1 stimulated **osteoblast** proliferation and new bone formation in cultures of calvarias from mice. These effects were blocked by endothelin A (ET(A)) but not by ET(B) receptor antagonists. Mice inoculated with the ZR-75-1 breast cancer line and treated with a selective ET(A) receptor antagonist (ABT-627) had significantly fewer **osteoblastic bone metastases** and less tumor burden compared with untreated mice. In contrast, there was no effect of ABT-627 on osteolytic **bone metastases** caused by ET-1-negative breast cancer, MDA-MB-231. ABT-627 had no effect on cell growth in vitro or at the orthotopic site (mammary fat pad) of ZR-75-1, or MDA-MB-231 cells. Collectively, the data suggest that tumor-produced ET-1 mediates **osteoblastic bone metastases** by stimulating **osteoblast** proliferation and new bone formation. Endothelin A receptor blockade may be useful for the prevention and treatment of **osteoblastic bone metastases** attributable to breast or prostate cancer.

L16 ANSWER 8 OF 8 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2003379832 EMBASE
TI A causal role for endothelin-1 in the pathogenesis of **osteoblastic bone metastases**.
AU Yin J.J.; Mohammad K.S.; Kakonen S.M.; Harris S.; Wu-Wong J.R.; Wessale J.L.; Padley R.J.; Garrett I.R.; Chirgwin J.M.; Guise T.A.
CS T.A. Guise, Department of Internal Medicine, Division of Endocrinology, University of Virginia, P.O. Box 801419, Charlottesville, VA 22908, United States. tag4n@virginia.edu
SO Proceedings of the National Academy of Sciences of the United States of America, (16 Sep 2003) 100/19 (10954-10959).
Refs: 42
ISSN: 0027-8424 CODEN: PNASA6
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
016 Cancer
037 Drug Literature Index
LA English
SL English
AB **Osteoblastic bone metastases** are common in prostate and breast cancer patients, but mechanisms by which tumor cells stimulate new bone formation are unclear. We identified three breast cancer cell lines that cause **osteoblastic** metastases in a mouse model and secrete endothelin-1. Tumor-produced endothelin-1 stimulates new bone formation in vitro and **osteoblastic** metastases in vivo via the endothelin A receptor. Treatment with an orally active endothelin A receptor antagonist dramatically decreased **bone metastases** and tumor burden in mice inoculated with ZR-75-1 cells. Tumor-produced endothelin-1 may have a major role in the establishment of

osteoblastic bone metastases, and endothelin A receptor blockade represents effective treatment.

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L3             0 S 19570407204/RN
L4             1 S 195704-72-4/RN
L5             1 S 178738-96-0/RN
L6             1 S 173937-92-3/RN
L7             1 S 173937-91-2/RN
L8             1 S 173864-34-1
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L10            7 S L1 OR L2 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9

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      MEDLINE, CANCERLIT' ENTERED AT 17:20:21 ON 31 AUG 2004
L11          581 S L10
L12        31827 S BONE# METASTA?
L13        81268 S OSTEOBLAST?
L14           30 S L11 AND L12
L15            9 S L11 AND L13
L16            8 S L14 AND L15

      FILE 'REGISTRY' ENTERED AT 17:23:12 ON 31 AUG 2004
L17            1 DUPLICATE REMOVE L8 (0 DUPLICATES REMOVED)

      FILE 'USPATFULL, BIOTECHNO, BIOSIS, EMBASE' ENTERED AT 17:23:43 ON 31 AUG
      2004

      FILE 'REGISTRY' ENTERED AT 17:23:44 ON 31 AUG 2004
L18            0 S L14 OR L15

      FILE 'CAPLUS, USPATFULL, BIOTECHNO, BIOSIS, EMBASE, TOXCENTER' ENTERED AT
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      FILE 'REGISTRY' ENTERED AT 17:27:19 ON 31 AUG 2004

      FILE 'CAPLUS, USPATFULL, BIOTECHNO, BIOSIS, EMBASE' ENTERED AT 17:28:38
      ON 31 AUG 2004

      FILE 'REGISTRY' ENTERED AT 17:28:40 ON 31 AUG 2004

      FILE 'USPATFULL, BIOTECHNO, BIOSIS, EMBASE' ENTERED AT 17:28:49 ON 31 AUG
      2004

      FILE 'REGISTRY' ENTERED AT 17:28:51 ON 31 AUG 2004

=> s endothelin antagonist#
          1063 ENDOTHELIN
           604 ANTAGONIST#
L19          0 ENDOTHELIN ANTAGONIST#
                 (ENDOTHELIN(W)ANTAGONIST#)

=> s endothelin antagonists
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             0 ANTAGONISTS
L20          0 ENDOTHELIN ANTAGONISTS
                 (ENDOTHELIN(W)ANTAGONISTS)

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COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              23.60     207.06
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                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00      -3.50

FILE 'CAPLUS' ENTERED AT 17:37:30 ON 31 AUG 2004
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FILE 'EMBASE' ENTERED AT 17:37:30 ON 31 AUG 2004
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FILE 'TOXCENTER' ENTERED AT 17:37:30 ON 31 AUG 2004
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FILE 'CANCERLIT' ENTERED AT 17:37:30 ON 31 AUG 2004

=> s endothelin antagonist#
L21        2727 ENDOTHELIN ANTAGONIST#

=> d his

     (FILE 'HOME' ENTERED AT 17:14:39 ON 31 AUG 2004)

     FILE 'REGISTRY' ENTERED AT 17:14:48 ON 31 AUG 2004
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L3             0 S 19570407204/RN
L4             1 S 195704-72-4/RN
L5             1 S 178738-96-0/RN
L6             1 S 173937-92-3/RN
L7             1 S 173937-91-2/RN
L8             1 S 173864-34-1
L9             1 S 173864-01-2/RN
L10            7 S L1 OR L2 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9

     FILE 'CAPLUS, USPATFULL, BIOTECHNO, IPA, BIOSIS, EMBASE, TOXCENTER,
     MEDLINE, CANCERLIT' ENTERED AT 17:20:21 ON 31 AUG 2004
L11          581 S L10
L12        31827 S BONE# METASTA?
L13        81268 S OSTEOBLAST?
L14           30 S L11 AND L12
L15            9 S L11 AND L13
L16            8 S L14 AND L15

     FILE 'REGISTRY' ENTERED AT 17:23:12 ON 31 AUG 2004
L17            1 DUPLICATE REMOVE L8 (0 DUPLICATES REMOVED)

     FILE 'USPATFULL, BIOTECHNO, BIOSIS, EMBASE' ENTERED AT 17:23:43 ON 31 AUG
     2004

     FILE 'REGISTRY' ENTERED AT 17:23:44 ON 31 AUG 2004
L18            0 S L14 OR L15
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FILE 'CAPLUS, USPATFULL, BIOTECHNO, BIOSIS, EMBASE, TOXCENTER' ENTERED AT 17:27:16 ON 31 AUG 2004

FILE 'REGISTRY' ENTERED AT 17:27:19 ON 31 AUG 2004

FILE 'CAPLUS, USPATFULL, BIOTECHNO, BIOSIS, EMBASE' ENTERED AT 17:28:38 ON 31 AUG 2004

FILE 'REGISTRY' ENTERED AT 17:28:40 ON 31 AUG 2004

FILE 'USPATFULL, BIOTECHNO, BIOSIS, EMBASE' ENTERED AT 17:28:49 ON 31 AUG 2004

FILE 'REGISTRY' ENTERED AT 17:28:51 ON 31 AUG 2004
L19 0 S ENDOTHELIN ANTAGONIST#
L20 0 S ENDOTHELIN ANTAGONISTS

FILE 'CAPLUS, USPATFULL, BIOTECHNO, BIOSIS, EMBASE, TOXCENTER, CANCERLIT' ENTERED AT 17:37:30 ON 31 AUG 2004
L21 2727 S ENDOTHELIN ANTAGONIST#

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4 FILES SEARCHED...
L22 3935754 CANCER OR CARCINOMA OR NEOPLASM

=> s prostate
L23 271186 PROSTATE

=> s l22 and l23
L24 200209 L22 AND L23

=> s l21 and l24
L25 148 L21 AND L24

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KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n
PROCESSING COMPLETED FOR L25
L26 128 DUPLICATE REMOVE L25 (20 DUPLICATES REMOVED)

=> s l26 and py<=2000
4 FILES SEARCHED...
5 FILES SEARCHED...
L27 32 L26 AND PY<=2000

=> d 1-32 bib abs

L27 ANSWER 1 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:115731 CAPLUS
DN 132:166247
TI Preparation of pyrimidinyloxypropanoates and related compounds as **endothelin antagonists**.
IN Amberg, Wilhelm; Jansen, Rolf; Kettschau, Georg; Hergenroeder, Stefan; Raschack, Manfred; Unger, Liliane
PA BASF A.-G., Germany
SO Ger. Offen., 18 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19836044	A1	20000217	DE 1998-19836044	19980810 <--
	CA 2340167	AA	20000224	CA 1999-2340167	19990807 <--

	WO 2000009489	A1	20000224	WO 1999-EP5728	19990807 <--
	W: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HR, HU, ID, IL, IN, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9953741	A1	20000306	AU 1999-53741	19990807 <--
	BR 9912889	A	20010508	BR 1999-12889	19990807
	EP 1104410	A1	20010606	EP 1999-939457	19990807
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	TR 200100427	T2	20010723	TR 2001-200100427	19990807
	JP 2002522531	T2	20020723	JP 2000-564942	19990807
	NO 2001000622	A	20010206	NO 2001-622	20010206
	BG 105236	A	20011231	BG 2001-105236	20010209
	HR 2001000164	A1	20020430	HR 2001-164	20010308
	ZA 2001001975	A	20020311	ZA 2001-1975	20010309
PRAI	DE 1998-19836044	A	19980810		
	WO 1999-EP5728	W	19990807		

OS MARPAT 132:166247

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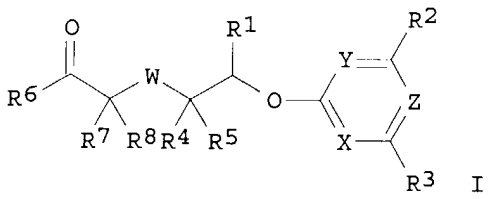

I

AB Title compds. [I; R1 = tetrazolyl, RCO; R = OR9, heteroaryl, etc.; R9 = H, cation, ammonium, alkyl, cycloalkyl, etc.; R2 = H, OH, amino, halo, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, alkylthio, etc.; X, Y = N, CH; Z = N, CR12; R12 = H, alkyl; R2R12, R3R12 = atoms to form (substituted) (O-, S-, or imino-interrupted) 5-6 membered alkylene, alkenylene; R3 = H, OH, imino, halo, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, haloalkoxy, alkylthio; R4, R5 = (substituted) Ph, naphthyl, etc.; R6 = (substituted) alkyl, Ph, naphthyl, heteroaryl; R7, R8 = H, alkyl; W = O, S], were prepared as **endothelin antagonists** (no data). Thus, 2-phenyl-1,3-dioxolan-2-ylmethanol, Me 3,3-diphenyl-2,3-epoxypropionate, and TsOH were stirred in CH2Cl2 at 0° for 15 min. to give Me 2-hydroxy-3,3-diphenyl-3-(2-phenyl-1,3-dioxolan-2-ylmethoxy)propionate. This was saponified with NaOH in dioxane/H2O and the acid in DMF was treated with NaH and 2-methanesulfonyl-4,6-dimethylpyrimidine to give 2-(4-methoxy-6-methylpyrimidin-2-yloxy)-3,3-diphenyl-3-(2-phenyl-1,3-dioxolan-2-ylmethoxy)propionic acid. The latter was stirred with TsOH in dioxane/H2O to give 2-(4-methoxy-6-methylpyrimidin-2-yloxy)-3-(2-oxo-2-phenylethoxy)-3,3-diphenylpropionic acid.

L27 ANSWER 2 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:576917 CAPLUS
DN 131:199706
TI Preparation of pyrimidinyloxyphenylbutyrates as mixed endothelin ETA/ETB receptor antagonists.
IN Amberg, Wilhelm; Jansen, Rolf; Klinge, Dagmar; Riechers, Hartmut; Hergenroder, Stefan; Raschack, Manfred; Unger, Liliane
PA Basf A.-G., Germany
SO PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DT Patent
LA German

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9944998	A1	19990910	WO 1999-EP1208	19990225 <--
	W: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HR, HU, ID, IL, IN, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	DE 19809144	A1	19990909	DE 1998-19809144	19980304 <--
	CA 2322541	AA	19990910	CA 1999-2322541	19990225 <--
	AU 9926247	A1	19990920	AU 1999-26247	19990225 <--
	BR 9908401	A	20001031	BR 1999-8401	19990225 <--
	TR 200002545	T2	20001121	TR 2000-200002545	19990225 <--
	EP 1060167	A1	20001220	EP 1999-906251	19990225 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, FI, RO				
	JP 2002505324	T2	20020219	JP 2000-534541	19990225
	ZA 9901738	A	20001011	ZA 1999-1738	19990304 <--
	TW 509676	B	20021111	TW 1999-88103317	19990304
	NO 2000004351	A	20000901	NO 2000-4351	20000901 <--
	BG 104754	A	20010531	BG 2000-104754	20000907
	HR 2000000650	A1	20010630	HR 2000-650	20001003
PRAI	DE 1998-19809144	A	19980304		
	WO 1999-EP1208	W	19990225		

OS MARPAT 131:199706

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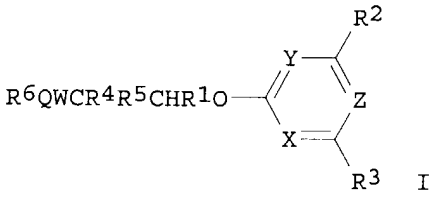

I

AB Title compds. [I; R1 = tetrazolyl, acyl; R2 = H, OH, amino, halo, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, haloalkoxy, alkylthio, etc.; X, Y = N, CH; Z = N, CR10; R10 = H, halo, OH, haloalkyl, alkyl; R2R10, R3R10 = atoms to form 5-6 membered rings; R3 = H, OH, amino, halo, alkyl, alkenyl, alkynyl, hydroxyalkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio; R4 = (substituted) alkyl, alkenyl, alkynyl; R5 = (substituted) Ph, naphthyl which may be bonded to R4; R6 = (substituted) cycloalkyl, Ph, naphthyl; W = O, S; Q = spacer], were prepared Thus, 2-hydroxy-3-[2-(4-chlorophenyl)ethoxy]-3-phenylbutyric acid (preparation given) was stirred with NaH in DMF followed by treatment with 2-chloro-4,6-dimethylpyrimidine followed by stirring for 4 days to give 2-(4,6-dimethylpyrimidin-2-yloxy)-3-[2-(4-chlorophenyl)ethoxy]-3-phenylbutyric acid. The latter bound to ETA and EtB receptors with Ki = 20 nM and 70 nM, resp.

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 3 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:254080 CAPLUS
DN 130:252685
TI Preparation of **endothelin antagonists** and their use as medicaments
IN Puhl, Michael; Amberg, Wilhelm; Hillen, Heinz; Kling, Andreas; Hergenroeder, Stefan; Markert, Claus Otto

PA BASF A.-G., Germany
SO Ger. Offen., 10 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19745151	A1	19990415	DE 1997-19745151	19971014 <--
	WO 9919346	A1	19990422	WO 1998-EP5943	19980918 <--
	W: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HU, ID, IL, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9896264	A1	19990503	AU 1998-96264	19980918 <--
	EP 1023318	A1	20000802	EP 1998-950050	19980918 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2001519440	T2	20011023	JP 2000-515917	19980918
	ZA 9809313	A	20000413	ZA 1998-9313	19981013 <--
PRAI	DE 1997-19745151	A	19971014		
	WO 1998-EP5943	W	19980918		

OS MARPAT 130:252685
AB Title compds. PhCH2CH(SR2)CONHCH(R1)CONHCH(R)CO2H [(I); R = H, (substituted)(branched)alkyl, alkylaryl, alkyl-hetaryl, (substituted)aryl, (substituted)hetaryl; R1 = (substituted) 2-thienyl-Me, β-naphthyl-Me, N-Boc-indol-3-ylmethyl; R2 = H, (substituted)acyl], useful in the treatment of diseases associated with endothelin-binding, were prepared using solid-phase synthesis, and tested. Thus, L-phenylalanine, bound to polystyrol, was chain-extended using normal solid-phase protocols to give I [R = (S)-CH2PH; R1 = (R)-β-naphthyl-methyl; R2 = (X)-SH(II)](no details). In in vitro tests for endothelin-conversion enzyme inhibiting activity, II had IC50 of 5μg/mg.

L27 ANSWER 4 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:424233 CAPLUS
DN 129:81755
TI Preparation of pyridazinyloxy- and pyrazinyloxydiphenylalkanoic acids as endothelin receptor antagonists.
IN Amberg, Wilhelm; Jansen, Rolf; Kling, Andreas; Klinge, Dagmar; Riechers, Hartmut; Hergenroder, Stefan; Raschack, Manfred; Unger, Liliane
PA Basf A.-G., Germany
SO PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9827070	A1	19980625	WO 1997-EP6778	19971204 <--
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	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	DE 19652763	A1	19980625	DE 1996-19652763	19961218 <--
	DE 19700884	A1	19980716	DE 1997-19700884	19970113 <--
	AU 9856594	A1	19980715	AU 1998-56594	19971204 <--
	AU 740351	B2	20011101		
	EP 946524	A1	19991006	EP 1997-952876	19971204 <--
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	CN 1247533	A	20000315	CN 1997-181869	19971204 <--
	BR 9714047	A	20000509	BR 1997-14047	19971204 <--

	NZ 336157	A	20001027	NZ 1997-336157	19971204 <--
	JP 2001506243	T2	20010515	JP 1998-527247	19971204
	ZA 9711305	A	19990617	ZA 1997-11305	19971217 <--
	US 6448248	B1	20020910	US 1999-319876	19990614
	NO 9902976	A	19990617	NO 1999-2976	19990617 <--
	KR 2000057642	A	20000925	KR 1999-705445	19990617 <--
PRAI	DE 1996-19652763	A	19961218		
	DE 1997-19700884	A	19970113		
	WO 1997-EP6778	W	19971204		

OS MARPAT 129:81755

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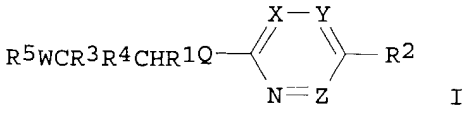

I

AB Title compds. [I; R1 = tetrazolyl, COR; R = OR6, 5-membered heteroaryl, etc.; R6 = H, alkali metal, alkaline earth metal, ammonium, cycloalkyl, alkyl, (substituted) PhCH2, etc.; R2 = (substituted) alkyl, alkenyl, alkynyl; R3, R4 = (substituted) Ph, naphthyl, cycloalkyl; R5 = H, (substituted) alkyl, alkenyl, alkynyl, Ph, naphthyl, 5-6 membered heterocyclyl; W = bond, O, S; Q = O, N; X = N, CH; Y = N, CR9; Z = N, CR10; R9, R10 = H, OH, amino, halo, alkoxy, haloalkoxy, alkylthio; with provisos], were prepared as endothelin receptor antagonists (no data). Thus, a suspension of NaH in DMF was treated dropwise with 2-hydroxy-3-methoxy-3,3-diphenylpropionic acid in DMF; 3-chloro-6-methylpyridazine in DMF was added and the mixture was stirred overnight to give 2-(6-methylpyridazin-3-yloxy)-3-methoxy-3,3-diphenylpropionic acid.

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 5 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN

AN 1997:684399 CAPLUS

DN 127:346381

TI Preparation of heterocyclyl ketoacids as **endothelin antagonists**

IN Cheng, Xue-Min; Doherty, Annette Marian; Hurley, Timothy Robert; Lovdahl, Michael James; Patt, William Chester; Repine, Joseph Thomas

PA Warner-Lambert Co., USA

SO PCT Int. Appl., 60 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9737987	A1	19971016	WO 1997-US3959	19970312 <--
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	AU 9725292	A1	19971029	AU 1997-25292	19970312 <--
	ZA 9703024	A	19971104	ZA 1997-3024	19970409 <--
	US 6043241	A	20000328	US 1998-117575	19980731 <--
PRAI	US 1996-15269P	P	19960410		
	WO 1997-US3959	W	19970312		

OS MARPAT 127:346381

GI

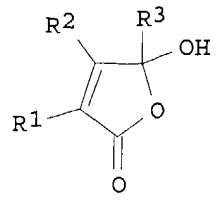
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I; R1 = H, alkyl, alkoxy, etc.; R2 = H, alkoxy; R3 = H, alkyl, alkoxy; R2R3 = OCH2O, OCH2CH2O; R4 = H, alkoxy; R5 = H, alkoxy, O-allyl; R6 = H, alkoxy, O-allyl; R7 = H, alkoxy, NH2, etc.; R5R6 = OCH2O; R6R7 = OCH2O; R8 = H, alkoxy; R9 = H, alkyl, alkoxy; R10 = alkoxy, amino; R9R10 = OCH2O; R11 = H, alkyl, alkoxy; R12 = H, alkoxy], novel nonpeptide antagonists of endothelin I which are useful in treating acute respiratory distress syndrome (ARDS), atherosclerosis, restenosis, Raynaud's phenomenon, chronic obstructive pulmonary diseases, mild or severe congestive heart failure, cerebral ischemia, cerebral infarction, embolic stroke, cerebral vasospasm, glaucoma, subarachnoid hemorrhage, hemorrhagic stroke, diabetes, gastric ulceration and mucosal damage, ischemic bowel disease, Crohn's disease, essential or malignant hypertension, pulmonary hypertension, pulmonary hypertension after bypass, male penile erectile dysfunction, **cancer**, especially malignant hemangioendothelioma or **prostate cancer**, myocardial infarction or ischemia, acute or chronic renal failure, renal ischemia, radiocontrast-induced nephrotoxicity, endotoxic, septic, hemorrhagic shock, angina, preeclampsia, asthma, arrhythmias, benign prostatic hyperplasia, and elevated levels or endothelin, were prepared by reacting an α-hydroxy butenolide II with one or more equivalent of a suitable base, and exposing the above mentioned solution to an UV light. Thus, compound (E)-I [R1 = H; R2R3 = OCH2O; R4 = R8 = H; R5-R7 = MeO; R9, R11, R12 = H; R10 = MeO] showed IC50 of 65 nM against HERBA-A (Ltk- cells expressing human ETAR).

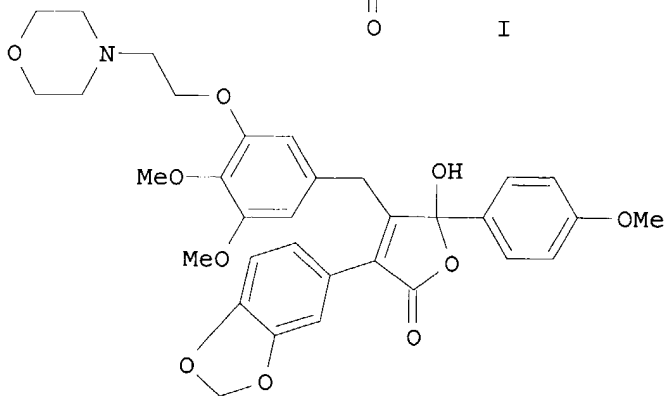
L27 ANSWER 6 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:684397 CAPLUS
DN 127:346287
TI Nonpeptide **endothelin antagonists** with increased water solubility
IN Cheng, Xue-Min; Doherty, Annette Marian; Patt, William Chester; Repine, Joseph Thomas
PA Warner-Lambert Co., USA
SO PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9737985	A1	19971016	WO 1997-US3929	19970312 <--
	W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9720778	A1	19971029	AU 1997-20778	19970312 <--
	ZA 9703026	A	19971104	ZA 1997-3026	19970409 <--
	US 6297274	B1	20011002	US 1998-117667	19980804
PRAI	US 1996-15242P	P	19960410		
	WO 1997-US3929	W	19970312		

OS MARPAT 127:346287
GI



I



II

AB Novel nonpeptide antagonists of endothelin are described, specifically the butenolides I [R1 = (un)substituted cycloalkyl, Ph, naphthyl, or heteroaryl; R2 = (un)substituted alkyl, cycloalkyl, aryl, or heteroaryl; R3 = (un)substituted alkyl, cycloalkyl, aryl, or heteroaryl; mol. bears at least 1 water solubility-enhancing substituent, and up to 4 total aqueous solubility groups; provided that when R2 = substituted alkyl, the substituent is not O located alpha to the furanone ring]. Also disclosed are methods for the preparation of I, and their pharmaceutical compns., which are useful in treating atherosclerosis, restenosis, Raynaud's phenomenon, mild or severe congestive heart failure, cerebral ischemia, cerebral infarction, embolic stroke, cerebral vasospasm, glaucoma, subarachnoid hemorrhage, hemorrhagic stroke, diabetes, gastric ulceration and mucosal damage, ischemic bowel disease, Crohn's disease, male penile erectile dysfunction, essential or malignant hypertension, pulmonary hypertension, pulmonary hypertension after bypass, **cancer**, especially malignant hemangioendothelioma or **prostate cancer**, myocardial infarction or ischemia, acute or chronic renal failure, renal ischemia, radiocontrast-induced nephrotoxicity, endotoxic, septic, or hemorrhagic shock, angina, preeclampsia, asthma, arrhythmias, benign prostatic hyperplasia, and elevated levels of endothelin. Example prepns. of 38 compds. and/or their salts, and 22 intermediates, are described. For instance, cyclocondensation of 2-benzo[1,3]dioxol-5-yl-4-(4-methoxyphenyl)-4-oxobutyric acid Me ester with 3-[2-(N-morpholinyl)ethoxy]-4,5-dimethoxybenzaldehyde in the presence of NaOMe, followed by treatment with AcOH, gave title compound II. In assays against human cloned receptors in vitro, II had IC50 values of 0.3 nM at ETA receptors and 2300 nM at ETB receptors. Aqueous solubility of I was excellent, with three representative compds. having solubility values of at least 25-80 mg/mL.

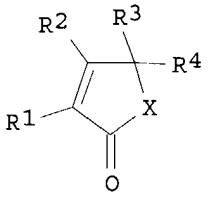
L27 ANSWER 7 OF 32 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1997:276449 CAPLUS
DN 126:251066
TI Preparation of furanones as **endothelin antagonists**
IN Cheng, Xue-Min; Doherty, Annette Marian; Patt, William Chester; Repine, Joseph Thomas
PA Warner-Lambert Company, USA
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DT Patent
LA English

FAN.CNT 1

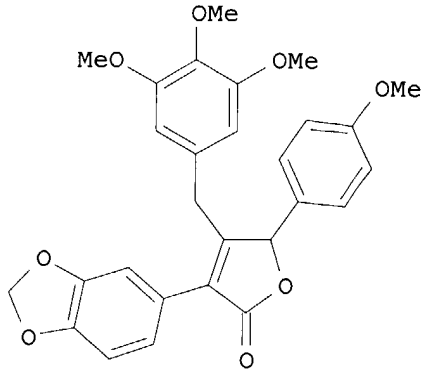
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9708169	A1	19970306	WO 1996-US12431	19960729 <--
	W: AU, BG, CA, CN, CZ, EE, GE, HU, IL, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, UA, US, UZ, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9666039	A1	19970319	AU 1996-66039	19960729 <--
	US 5998468	A	19991207	US 1997-983554	19971215 <--
PRAI	US 1995-2724P	P	19950824		
	WO 1996-US12431	W	19960729		

OS MARPAT 126:251066

GI



I



II

AB Novel nonpeptide antagonists of endothelin [I; R1 = (un)substituted C3-12 cycloalkyl, Ph, naphthyl, heteroaryl; R2 = (un)substituted C1-12 alkyl, C3-12 cycloalkyl; R3 = (un)substituted C1-12 alkyl, C3-12 cycloalkyl, etc.; R4 = OH, O(C1-7 alkyl), SH, etc.; X = O, S], useful in treating elevated levels of endothelin, acute and chronic renal failure, hypertension, myocardial infarction, myocardial ischemia, cerebral vasospasm, cerebral ischemia, cerebral infarction, cirrhosis, septic shock, congestive heart failure, endotoxic shock, subarachnoid hemorrhage, arrhythmias, asthma, preeclampsia, atherosclerotic disorders including Raynaud's disease and restenosis, angina, **cancer**, pulmonary hypertension, ischemic disease, gastric mucosal damage, hemorrhagic shock, ischemic bowel disease, stroke, benign prostatic hyperplasia (BPH), and diabetes, were prepared Thus, treatment of 3-(benzo[1,3]dioxol-5-yl)-5-hydroxy-5-(4-methoxyphenyl)-4-(3,4,5-trimethoxybenzyl)-5H-furan-2-one with CF3COOH followed by addition Et3SiH afforded II which showed IC50 of 30 nM against endothelin receptor ETA (ERBA-A) and of > 2500 nM against ETB (ERBA-B).

L27 ANSWER 8 OF 32 USPATFULL on STN

AN 2004:27131 USPATFULL

TI α-hydrdroxylic acid derivatives, their production and use

IN Klinge, Dagmar, Heidelberg, GERMANY, FEDERAL REPUBLIC OF
Amberg, Wilhelm, Friedrichsdorf, GERMANY, FEDERAL REPUBLIC OF
Baumann, Ernst, Dudenhofen, GERMANY, FEDERAL REPUBLIC OF
Kling, Andreas, Mannheim, GERMANY, FEDERAL REPUBLIC OF
Riechers, Hartmut, Neustadt, GERMANY, FEDERAL REPUBLIC OF
Unger, Liliane, Ludwigshafen, GERMANY, FEDERAL REPUBLIC OF
Raschack, Manfred, Weisenheim, GERMANY, FEDERAL REPUBLIC OF
Hergenroder, Stefan, Mainz, GERMANY, FEDERAL REPUBLIC OF
Schult, Sabine, Speyer, GERMANY, FEDERAL REPUBLIC OF

PA Abbott GmbH & Co., KG, Wiesbaden, GERMANY, FEDERAL REPUBLIC OF (non-U.S.

corporation)
PI US 6686369 B1 20040203
WO 9738981 19971023 <--
AI US 1998-155944 19981008 (9)
WO 1997-EP1688 19970404
PRAI DE 1996-19614533 19960412
DT Utility
FS GRANTED
EXNAM Primary Examiner: Shah, Mukund J.; Assistant Examiner: Balasubramanian, Venkataraman
LREP Wood, Phillips, Katz, Clark & Mortimer
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 1486
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to carboxylic acid derivatives of the formula ##STR1##

where the radicals have the meanings stated in the description, to the preparation of these compounds and to their use as drugs.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 9 OF 32 USPATFULL on STN
AN 2003:228330 USPATFULL
TI Carboxylic acid derivatives, their production and use
IN Riechers, Hartmut, Neustadt, GERMANY, FEDERAL REPUBLIC OF
Klinge, Dagmar, Heidelberg, GERMANY, FEDERAL REPUBLIC OF
Amberg, Wilhelm, Friedrichsdorf, GERMANY, FEDERAL REPUBLIC OF
Kling, Andreas, Mannheim, GERMANY, FEDERAL REPUBLIC OF
Hillen, Heinz, Hassloch, GERMANY, FEDERAL REPUBLIC OF
Unger, Liliane, Ludwigshafen, GERMANY, FEDERAL REPUBLIC OF
Elger, Bernd, Neustadt, GERMANY, FEDERAL REPUBLIC OF
PA BASF Aktiengesellschaft, Ludwigshafen, GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)
PI US 6610691 B1 20030826
WO 9738980 19971023 <--
AI US 1998-155946 19981008 (9)
WO 1997-EP1684 19970404
PRAI DE 1996-19614534 19960412
DT Utility
FS GRANTED
EXNAM Primary Examiner: Raymond, Richard L.; Assistant Examiner: Balasubramanian, Venkataraman
LREP Wood, Phillips, Katz, Clark & Mortimer
CLMN Number of Claims: 15
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 1298
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to carboxylic acid derivatives of the formula ##STR1##

where the radicals have the meanings defined in the description, to the preparation of these compounds and to their use as drugs.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 10 OF 32 USPATFULL on STN
AN 2001:168157 USPATFULL
TI Nonpeptide **endothelin antagonists** with increased water solubility
IN Cheng, Xue-Min, Ann Arbor, MI, United States

Doherty, Annette Marian, Ann Arbor, MI, United States
Patt, William Chester, Chelsea, MI, United States
Repine, Joseph Thomas, Ann Arbor, MI, United States
PA Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)
PI US 6297274 B1 20011002
WO 9737985 19971016
AI US 1998-117667 19980804 (9)
WO 1997-US3929 19970312
19980804 PCT 371 date
19980804 PCT 102(e) date
DT Utility
FS GRANTED
EXNAM Primary Examiner: Mckane, Joseph K.; Assistant Examiner: Murray, Joseph
LREP Anderson, Elizabeth M., Kurlandsky, David R.
CLMN Number of Claims: 29
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2157
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Novel nonpeptide endothelin I antagonists of Formula ##STR1##

are described wherein R.sub.1 is unsubstituted or substituted cycloalkyl, phenyl, naphthyl or heteroaryl, R.sub.2 is unsubstituted or substituted alkyl, aryl or heteroaryl, R.sub.3 is unsubstituted or substituted alkyl, cycloalkyl, aryl or heteroayl, and R.sub.1 and/or R.sub.2 and/or R.sub.3 are independently substituted by a total of from 1 to 4 substituents which enhance aqueous solubility with the proviso that when R.sub.2 is alkyl and is substituted, the substituent is not oxygen at the α-position of the furanone ring. Further described are methods for the preparation and pharmaceutical compositions of compounds of Formula I, which are useful in treating atherosclerosis, restenosis, Raynaud's phenomenon, mild or severe congestive heart failure, cerebral ischemia, cerebral infarction, embolic stroke, cerebral vasospasm, glaucoma, subarachnoid hemorrhage, hemorrhagic stroke, diabetes, gastric ulceration and mucosal damage, ischemic bowel disease, Chrohn's disease, male penile erectile dysfunction, essential or malignant hypertension, pulmonary hypertension, pulmonary hypertension after bypass, **cancer**, especially malignant hemangioendothelioma or **prostate cancer**, myocardial infarction or ischemia, acute or chronic renal failure, renal ischemia, radiocontrast-induced nephrotoxcity, endotoxic, septic hemorrhagic shock, angina, preeclampsia, asthma, arrhythmias, benign prostatic hyperplasia, and elevated levels of endothelin.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 11 OF 32 USPATFULL on STN
AN 2000:171151 USPATFULL
TI **Endothelin antagonists**
IN Winn, Martin, Deerfield, IL, United States
Boyd, Steven A., Mundelein, IL, United States
Hutchins, Charles W., Gurnee, IL, United States
Jae, Hwan-Soo, Glencoe, IL, United States
Tasker, Andrew S., Gurnee, IL, United States
von Geldern, Thomas W., Richmond, IL, United States
Kester, Jeffrey A., Deerfield, IL, United States
Sorensen, Bryan K., Waukegan, IL, United States
Szczepankiewicz, Bruce G., Gages Lake, IL, United States
Henry, Kenneth J., Waukegan, IL, United States
Liu, Gang, Gurnee, IL, United States
Wittenberger, Steven J., Mundelein, IL, United States
King, Steven A., Gurnee, IL, United States
PA Abbott Laboratories, Abbott Park, IL, United States (U.S. corporation)

PI US 6162927 20001219 <--
AI US 1997-905913 19970804 (8)
RLI Continuation-in-part of Ser. No. US 1997-794506, filed on 4 Feb 1997 which is a continuation-in-part of Ser. No. US 1996-600625, filed on 13 Feb 1996, now abandoned which is a continuation-in-part of Ser. No. US 1995-497998, filed on 2 Aug 1995, now abandoned which is a continuation-in-part of Ser. No. US 1995-442575, filed on 30 May 1995, now patented, Pat. No. US 5767144 which is a continuation-in-part of Ser. No. US 1994-334717, filed on 4 Nov 1994, now abandoned which is a continuation-in-part of Ser. No. US 1994-293349, filed on 19 Aug 1994, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Higel, Floyd D.
LREP Strode, Janelle D.
CLMN Number of Claims: 10
ECL Exemplary Claim: 2,3
DRWN No Drawings
LN.CNT 13238
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A compound of the formula (I): ##STR1## or a pharmaceutically acceptable salt thereof is disclosed, as well as processes for and intermediates in the preparation thereof, and a method of antagonizing endothelin.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 12 OF 32 USPATFULL on STN
AN 2000:142385 USPATFULL
TI Annelated dihydropyridines and the use thereof for preparing pharmaceutical preparations
IN Roos, Otto, Schwabenheim, Germany, Federal Republic of
Losel, Walter, Gau-Algesheim, Germany, Federal Republic of
Arndts, Dietrich, Appenheim, Germany, Federal Republic of
PA Boehringer Ingelheim GmbH, Ingelheim, Germany, Federal Republic of (non-U.S. corporation)
PI US 6136819 20001024 <--
AI US 1999-329443 19990610 (9)
RLI Division of Ser. No. US 1997-857643, filed on 16 May 1997, now patented, Pat. No. US 5968948 which is a division of Ser. No. US 1994-360867, filed on 21 Dec 1994, now patented, Pat. No. US 5661157
PRAI DE 1993-4343683 19931221
DT Utility
FS Granted
EXNAM Primary Examiner: Davis, Zinna Northington
LREP Raymond, Robert P., Stempel, Alan R., Devlin, Mary-Ellen M.
CLMN Number of Claims: 5
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1199
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compound of general formula I ##STR1## wherein A denotes a benzo, indolo or thienyl group;

B denotes the group --O--, --S-- or --CHR.sup.5 --, wherein R.sup.5 is hydrogen, (C.sub.1 -.sub.6)alkyl, phenyl or benzyl;

R.sup.3 denotes 2- or 3-thienyl, (C.sub.4 -.sub.7)cycloalkyl, (C.sub.4 -.sub.6)cycloalkyl(C.sub.1 -.sub.5)alkyl or ##STR2## wherein R is (C.sub.1 -.sub.4)alkyl, hydroxy, --N.sub.3, halogen (F, Cl, Br, I), CF.sub.3 or (C.sub.1 -.sub.4)alkoxy,

u is 0, 1, 2 or 3, and

m, R.sup.2, R.sup.4, R.sup.7, R.sup.8 and R.sup.9 are as defined in the

specification, as well as pharmaceutical preparations containing these compounds and the pharmaceutical use thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 13 OF 32 USPATFULL on STN
AN 2000:138349 USPATFULL
TI **Endothelin antagonists** with ether-linked groups
IN Cheng, Xue-Min, Ann Arbor, MI, United States
Doherty, Annette Marian, Ann Arbor, MI, United States
Patt, William Chester, Chelsea, MI, United States
Repine, Joseph Thomas, Ann Arbor, MI, United States
PA Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)
PI US 6133263 20001017 <--
WO 9737986 19971016
AI US 1998-117649 19980803 (9)
WO 1997-US3930 19970312
19980803 PCT 371 date
19980803 PCT 102(e) date
PRAI US 1996-15238P 19960410 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Ramsuer, Robert W.
LREP Anderson, Elizabeth M.
CLMN Number of Claims: 30
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1439
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Novel nonpeptide **endothelin antagonists** with ether-linked groups are described, as well as methods for the preparation and pharmaceutical compositions of the same, which are useful in treating atherosclerosis, restenosis, Raynaud's phenomenon, mild or severe congestive heart failure, cerebral ischemia, cerebral infarction, embolic stroke, cerebral vasospasm, subarachnoid hemorrhage, hemorrhagic stroke, diabetes, gastric ulceration and mucosal damage, ischemnic bowel disease, Chrohn's disease, essential or malignant hypertension, pulmonary hypertension, pulmonary hypertension after bypass, acute respiratory distress syndrome, chronic obstructive pulmonary diseases, male penile erectile dysfunction, **cancer**, especially malignant hemangicendothelioma or **prostate cancer**, myocardial infarction or ischemia, acute or chronic renal failure, renal ischemia, radiocontrast-induced nepbrotoxicity, endotoxic, septic, hemorrhagic shock, angina, preeclampsia, asthma, arhythmias, benign prostatic hyperplasia, and elevated levels of endothelin.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 14 OF 32 USPATFULL on STN
AN 2000:128375 USPATFULL
TI Substituted phenyl compounds with a substituent having a thienyl ring
IN Smith, Christopher, Dagenham, United Kingdom
Porter, Barry, Dagenham, United Kingdom
Walsh, Roger, Dagenham, United Kingdom
Majid, Tahir, Dagenham, United Kingdom
McCarthy, Clive, Dagenham, United Kingdom
Harris, Neil, Dagenham, United Kingdom
Astles, Peter, Dagenham, United Kingdom
McLay, Iain, Dagenham, United Kingdom
Morley, Andrew, Dagenham, United Kingdom
Bridge, Andrew, Dagenham, United Kingdom
Van Sickle, Andrew, Dagenham, United Kingdom

Halley, Frank, Dagenham, United Kingdom
Roach, Alan, Dagenham, United Kingdom
Foster, Martyn, Dagenham, United Kingdom
PA Rhone-Poulenc Rorer Limited, West Malling, United Kingdom (non-U.S. corporation)
PI US 6124343 20000926 <--
AI US 1997-898547 19970722 (8)
RLI Continuation-in-part of Ser. No. WO 1996-GB120, filed on 22 Jan 1996
PRAI GB 1919-9501635 19190127
GB 1995-4061 19950301
GB 1995-9604 19950511
GB 1996-15752 19960726
US 1996-24902P 19960830 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Stockton, Laura L.
LREP Synnestvedt & Lechner LLP
CLMN Number of Claims: 19
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3327
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention is directed to compounds of formula I ##STR1## wherein R.sup.1 is CN, CH.sub.2 CN, CH.dbd.CHCN, CHO, or CH.dbd.CHCO.sub.2 H;

R.sup.2 is aryl lower alkoxy, heteroaryl lower alkoxy, aryl lower alkylthio or heteroaryl lower alkylthio wherein each of the aryl and heteroaryl moieties is optionally substituted;

R.sup.3 is halogen;

R.sup.4 is optionally substituted aryl or optionally substituted heteroaryl;

R.sup.5 is carboxy or an acid isostere;

X is oxygen or sulphur; and

n is zero or 1; or an N-oxide thereof, prodrug thereof solvate thereof, or pharmaceutically acceptable salt thereof, which compounds have **endothelin antagonist** activity. The invention is also directed to methods for preparing the compounds of formula I and their pharmaceutical use.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 15 OF 32 USPATFULL on STN
AN 2000:105915 USPATFULL
TI Carboxylic acid derivatives, their production and use
IN Amberg, Wilhelm, Friedrichsdorf, Germany, Federal Republic of
Kling, Andreas, Mannheim, Germany, Federal Republic of
Klinge, Dagmar, Heidelberg, Germany, Federal Republic of
Riechers, Hartmut, Neustadt, Germany, Federal Republic of
Baumann, Ernst, Dudenhofen, Germany, Federal Republic of
Unger, Liliane, Ludwigshafen, Germany, Federal Republic of
Raschack, Manfred, Weisenheim, Germany, Federal Republic of
Hergenroder, Stefan, Mainz, Germany, Federal Republic of
Schult, Sabine, Speyer, Germany, Federal Republic of
PA BASF Aktiengesellschaft, Ludwigshafen, Germany, Federal Republic of (non-U.S. corporation)
PI US 6103732 20000815 <--
WO 9738982 19971023 <--
AI US 1998-155948 19981008 (9)
WO 1997-EP1687 19970404

19981008 PCT 371 date
19981008 PCT 102(e) date
PRAI DE 1996-19614542 19960412
DT Utility
FS Granted
EXNAM Primary Examiner: Shah, Mukund J.; Assistant Examiner: Balasubramanian, V.
LREP Keil & Weinkauf
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1074
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Carboxylic acid derivatives of the formula I ##STR1## where the radicals have the meanings stated in the description, and the preparation of these agreements [sic] and their use as drugs are described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 16 OF 32 USPATFULL on STN
AN 2000:88197 USPATFULL
TI Quinazolinone inhibitors of cGMP phosphodiesterase
IN Macor, John E., Flemington, NJ, United States
Rotella, David P., Newtown, PA, United States
Weller, III, Harold N., Pennington, NJ, United States
Cushman, David W., Lawrenceville, NJ, United States
Yevich, Joseph P., Southington, CT, United States
PA Bristol-Myers Squibb Company, Princeton, NJ, United States (U.S. corporation)
PI US 6087368 20000711 <--
AI US 1999-322678 19990528 (9)
PRAI US 1998-88538P 19980608 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Shah, Mukund J.; Assistant Examiner: Balasubramanian, V
LREP Davis, Stephen B., Babajko, Suzanne
CLMN Number of Claims: 17
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3144
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Novel quinazolinone compounds, methods of using such compounds in the treatment of cGMP-associated conditions such as erectile dysfunction, and pharmaceutical compositions containing such compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 17 OF 32 USPATFULL on STN
AN 2000:61727 USPATFULL
TI Methods and compositions for treatment of cell proliferative disorders
IN Vournakis, John N., Charleston, SC, United States
Finkielsztein, Sergio, Chestnut Hill, MA, United States
Pariser, Ernest R., Belmont, MA, United States
PA Marine Polymer Technologies, Inc., Danvers, MA, United States (U.S. corporation)
PI US 6063911 20000516 <--
AI US 1998-218288 19981222 (9)
RLI Continuation-in-part of Ser. No. US 1995-471290, filed on 6 Jun 1995, now patented, Pat. No. US 5858350 which is a continuation-in-part of Ser. No. US 1994-347911, filed on 1 Dec 1994, now patented, Pat. No. US 5623064 which is a continuation-in-part of Ser. No. US 1993-160569, filed on 1 Dec 1993, now patented, Pat. No. US 5622834
DT Utility

FS Granted
EXNAM Primary Examiner: Lankford, Jr., Leon B.; Assistant Examiner: Tate, Christopher R.
LREP Pennie & Edmonds LLP
CLMN Number of Claims: 35
ECL Exemplary Claim: 1
DRWN 15 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 2018
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to methods and compositions comprising at least one **endothelin antagonist**, preferably in combination with a poly-β-1→4-N-acetylglucosamine (p-GlcNAc) polysaccharide matrix, for use in the treatment of **cancer** and other proliferative diseases. The **endothelin antagonist** can be a peptide or non-peptide compound, and the p-GlcNAc matrix of the invention is comprised of a polymer of high molecular weight whose constituent monosaccharide sugars are attached in a β-1→4 conformation, and which is free of proteins, and substantially free of single amino acids, and other organic and inorganic contaminants. The compositions and methods of the invention are useful for inhibiting the growth of tumors and other neoplastic cells and/or for inhibiting the metastasis of neoplastic cells in vivo.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 18 OF 32 USPATFULL on STN
AN 2000:44132 USPATFULL
TI Substituted phenyl compounds with a substituent having A 1,3-benzodioxole ring
IN Smith, Christopher, Dagenham, United Kingdom
Porter, Barry, Dagenham, United Kingdom
Walsh, Roger, Dagenham, United Kingdom
Majid, Tahir, Dagenham, United Kingdom
McCarthy, Clive, Dagenham, United Kingdom
Harris, Neil, Dagenham, United Kingdom
Astles, Peter, Dagenham, United Kingdom
McLay, Iain, Dagenham, United Kingdom
Morley, Andrew, Dagenham, United Kingdom
Bridge, Andrew, Dagenham, United Kingdom
Van Sickle, Andrew, Dagenham, United Kingdom
Halley, Frank, Dagenham, United Kingdom
Roach, Alan, Dagenham, United Kingdom
Foster, Martyn, Dagenham, United Kingdom
PA Rhone-Poulenc Rorer Limited, West Malling, United Kingdom (non-U.S. corporation)
PI US 6048893 20000411 <--
AI US 1999-330288 19990611 (9)
RLI Division of Ser. No. US 1997-898547, filed on 22 Jul 1997 which is a continuation-in-part of Ser. No. WO 1996-GB120, filed on 22 Jan 1996
PRAI GB 1995-1635 19950127
GB 1995-4061 19950301
GB 1995-9604 19950511
GB 1996-15752 19960726
US 1996-24902P 19960830 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Stockton, Laura L.
LREP Oehler, Ross J.
CLMN Number of Claims: 23
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3342
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention is directed to compounds of formula I ##STR1## wherein

R.sup.1 is CN, CH.sub.2 CN, CH.dbd.CHCN, CHO, or CH.dbd.CHCO.sub.2 H;

R.sup.2 is aryl lower alkoxy, heteroaryl lower alkoxy, aryl lower alkylthio or heteroaryl lower alkylthio wherein each of the aryl and heteroaryl moieties is optionally substituted;

R.sup.3 is halogen;

R.sup.4 is optionally substituted aryl or optionally substituted heteroaryl;

R.sup.5 is carboxy or an acid isostere;

X is oxygen or sulphur; and

n is zero or 1; or an N-oxide thereof, prodrug thereof solvate thereof, or pharmaceutically acceptable salt thereof, which compounds have **endothelin antagonist** activity. The invention is also directed to methods for preparing the compounds of formula I and their pharmaceutical use.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 19 OF 32 USPATFULL on STN
AN 2000:37797 USPATFULL
TI Ketoacid **endothelin antagonists**
IN Cheng, Xue-Min, Ann Arbor, MI, United States
Doherty, Annette Marian, Paris, France
Hurley, Timothy Robert, Ann Arbor, MI, United States
Lovdahl, Michael James, Ann Arbor, MI, United States
Patt, William Chester, Chelsea, MI, United States
Repine, Joseph Thomas, Ann Arbor, MI, United States
PA Warner-Lambert Company, Morris Plains, NJ, United States (U.S. corporation)
PI US 6043241 20000328 <--
WO 9737987 19971016
AI US 1998-117575 19980731 (9)
WO 1997-US3959 19970312
19980731 PCT 371 date
19980731 PCT 102(e) date
PRAI US 1996-15269P 19960410 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Powers, Fiona T.
LREP Anderson, Elizabeth M.
CLMN Number of Claims: 32
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1330
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compounds of the Formula I ##STR1## are nonpeptide antagonists of endothelin which are useful in treating a variety of diseasses such as elevated levels of endothelin, acute respiratory distress syndrome (ARDS), atherosclerosis, restenosis, Raynaud's phenomenon etc. The compounds are prepared by reacting an alpha-hydroxy butenolide with one or more equivalents of a suitable base, and exposing the solution to UV light.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 20 OF 32 USPATFULL on STN
AN 2000:24649 USPATFULL
TI Carboxylic acid derivatives, their preparation and use in treating **cancer**

IN Romerdahl, Cynthia A., Wayland, MA, United States
PA BASF Aktiengesellschaft, Germany, Federal Republic of (non-U.S. corporation)
PI US 6030975 20000229 <--
AI US 1997-818622 19970314 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Goldberg, Jerome D.
LREP Hamilton, Brook, Smith & Reynolds, P.C.
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2911
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides a method for treating **cancer** in an individual, wherein the **cancer** is a tumor in which endothelin is upregulated (e.g. tumors of the **prostate**, lung, liver, breast, brain, stomach, colon, endometrium, testicle, thyroid, pituatary, bladder, kidney, pancreas and meninges) by administering to the individual an effective amount of a compound of Formula I or Formula Ia, as describe herein.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 21 OF 32 USPATFULL on STN
AN 1999:128564 USPATFULL
TI Annelated dihydropyridines and the use thereof for preparing pharmaceutical preparations
IN Roos, Otto, Schwabenheim, Germany, Federal Republic of
Losel, Walter, Gau-Algesheim, Germany, Federal Republic of
Arndts, Dietrich, Appenheim, Germany, Federal Republic of
PA Boerhinger Ingelheim GmbH, Ingelheim am Rhein, Germany, Federal Republic of (non-U.S. corporation)
PI US 5968948 19991019 <--
AI US 1997-857643 19970516 (8)
RLI Division of Ser. No. US 1994-360867, filed on 21 Dec 1994, now patented, Pat. No. US 5661157
PRAI DE 1993-4343683 19931221
DT Utility
FS Granted
EXNAM Primary Examiner: Davis, Zinna Northington
LREP Raymond, Robert P., Stempel, Alan R., Devlin, Mary-Ellen
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1226
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compound of general formula I ##STR1## wherein A denotes a benzo, indolo or thienyl group;

B denotes the group --O--, --S-- or --CHR.sup.5 --, wherein R.sup.5 is hydrogen, (C.sub.1-6)alkyl, phenyl or benzyl;

R.sup.3 denotes 2- or 3-thienyl, (C.sub.4-7)cycloalkyl, (C.sub.4-6)cycloalkyl(C.sub.1-5)alkyl or ##STR2## wherein R is (C.sub.1-4)alkyl, hydroxy, --N.sub.3, halogen (F, Cl, Br, I), CF.sub.3 or (C.sub.1-4)alkoxy,

u is 0, 1, 2 or 3, and

m, R.sup.2, R.sup.4, R.sup.7, R.sup.8 and R.sup.9 are as defined in the specification, as well as pharmaceutical preparations containing these compounds and the pharmaceutical use thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 22 OF 32 USPATFULL on STN
AN 1999:81842 USPATFULL
TI Annelated dihydropyridines and the use thereof for preparing pharmaceutical preparations
IN Losel, Walter, Gau-Algesheim, Germany, Federal Republic of
Roos, Otto, Schwabenheim, Germany, Federal Republic of
Arndts, Dietrich, Appenheim, Germany, Federal Republic of
PA Boehringer Ingelheim KG, Ingelheim am Rhein, Germany, Federal Republic of (non-U.S. corporation)
PI US 5925650 19990720 <--
AI US 1997-993855 19971218 (8)
RLI Continuation of Ser. No. US 1995-465637, filed on 5 Jun 1995, now patented, Pat. No. US 5837712 which is a continuation of Ser. No. US 1994-360524, filed on 21 Dec 1994, now patented, Pat. No. US 5607943
PRAI DE 1993-4343684 19931221
DE 1993-4343641 19931221
DT Utility
FS Granted
EXNAM Primary Examiner: Raymond, Richard L.; Assistant Examiner: Kessinger, Ann M.
LREP Raymond, Robert P., Stempel, Alan R., Bottino, Anthony P.
CLMN Number of Claims: 2
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 986
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A compound of formula I ##STR1## wherein A denotes a benzo, indolo or thieno group;

R.sup.1 denotes thienyl or the group ##STR2## wherein R.sup.7, R.sup.8 and R.sup.9 independently of one another may represent methyl, ethyl, propyl, phenyl or benzyl, whilst not more than 2 of the substituents can simultaneously represent phenyl or benzyl;

R.sup.2, m, R.sup.3 and R.sup.4 are defined as in the specification, as well as pharmaceutical preparations containing this compound and the new pharmaceutical uses thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 23 OF 32 USPATFULL on STN
AN 1999:7399 USPATFULL
TI Dihydro-isoquinoline compounds and their use as pharmaceuticals
IN Arndts, Dietrich, Appenheim, Germany, Federal Republic of
Losel, Walter, Gau-Algesheim, Germany, Federal Republic of
Roos, Otto, Schwabenheim, Germany, Federal Republic of
PA Boehringer Ingelheim KG, Ingelheim, Germany, Federal Republic of (non-U.S. corporation)
PI US 5861412 19990119 <--
AI US 1997-872584 19970610 (8)
RLI Continuation of Ser. No. US 1995-478298, filed on 6 Jun 1995, now abandoned which is a division of Ser. No. US 1994-249822, filed on 26 May 1994, now abandoned which is a continuation of Ser. No. US 1993-81599, filed on 22 Jun 1993, now abandoned
PRAI DE 1992-4220353 19920622
DE 1992-4220319 19920622
DE 1992-4220355 19920622
DE 1992-4220368 19920622
DE 1992-4220345 19920622
DE 1992-4220312 19920622
DE 1992-4220373 19920622
DE 1992-4220369 19920622

DT Utility
FS Granted
EXNAM Primary Examiner: Kight, John; Assistant Examiner: Mach, D. Margaret M.
LREP Raymond, R. P., Devlin, M-E. M., Stempel, A. R.
CLMN Number of Claims: 6
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1716
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compound of general formula I ##STR1## wherein A is a benzo or thieno group;

R.sub.1 is (C.sub.4-6)cycloalkyl, (C.sub.4-6)cycloalkyl-(C.sub.1-5)alkyl or ##STR2## R.sup.2, m, R.sup.3, R.sup.4, R and u are defined as in the specification, and pharmaceutical preparations containing this compound and the new pharmaceutical uses thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 24 OF 32 USPATFULL on STN
AN 1998:144111 USPATFULL
TI Annelated dihydropyridines and the use thereof for preparing pharmaceutical preparations
IN Losel, Walter, Gau-Algesheim, Germany, Federal Republic of
Roos, Otto, Schwabenheim, Germany, Federal Republic of
Arndts, Dietrich, Appenheim, Germany, Federal Republic of
PA Boehringer Ingelheim KG, Ingelheim am Rhein, Germany, Federal Republic of (non-U.S. corporation)
PI US 5837712 19981117 <--
AI US 1995-465637 19950605 (8)
RLI Continuation of Ser. No. US 1994-360524, filed on 21 Dec 1994, now patented, Pat. No. US 5607943
PRAI DE 1993-4343684 19931221
DE 1993-4343641 19931221
DT Utility
FS Granted
EXNAM Primary Examiner: Ford, John M.; Assistant Examiner: Wong, King Lit
LREP Raymond, Robert P., Stempel, Alan R., Devlin, Mary-Ellen
CLMN Number of Claims: 7
ECL Exemplary Claim: 4
DRWN No Drawings
LN.CNT 1035
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A compound of formula I ##STR1## wherein A denotes a benzo, indolo or thieno group;

R.sup.1 denotes thienyl or the group ##STR2## wherein R.sup.7, R.sup.8 and R.sup.9 independently of one another may represent methyl, ethyl, propyl, phenyl or benzyl, while not more than 2 of the substituents can simultaneously represent phenyl or benzyl;

R.sup.2, m, R.sup.3 and R.sup.4 are defined as in the specification, as well as pharmaceutical preparations containing this compound and the new pharmaceutical uses thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 25 OF 32 USPATFULL on STN
AN 97:107079 USPATFULL
TI Pyridazino[4',5':3,4]pyrrolo-[2,1-a]-isoquinolines and the use thereof for preparing pharmaceutical preparations
IN Losel, Walter, Gau-Algesheim, Germany, Federal Republic of
Roos, Otto, Schwabenheim, Germany, Federal Republic of
Arndts, Dietrich, Appenheim, Germany, Federal Republic of

PA Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany, Federal Republic of (non-U.S. corporation)
PI US 5688793 19971118 <--
AI US 1996-699809 19960819 (8)
RLI Continuation of Ser. No. US 1994-360863, filed on 21 Dec 1994, now abandoned
PRAI DE 1993-4343649 19931221
DT Utility
FS Granted
EXNAM Primary Examiner: Bernhardt, Emily
LREP Raymond, Robert P., Stempel, Alan R., Devlin, Mary-Ellen
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 851
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to new pyridazino[4',5':3,4]-pyrrolo[2,1-a]isoquinolines of the formula ##STR1## and the physiologically acceptable salts thereof with acids and complex-forming agents, wherein X is O, S or NHO and R.sub.1, R.sub.3, R.sub.4, R.sub.5, R.sub.6, R.sub.7, R.sub.8 and R.sub.9 are defined as in the specification, and pharmaceutical preparations containing these compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 26 OF 32 USPATFULL on STN
AN 97:94236 USPATFULL
TI 9-amino-pyridazino[4'5':3,4]pyrrolo-[2,1-a]isoquinolines and the use thereof for the production of pharmaceutical preparations
IN Arndts, Dietrich, Appenheim, Germany, Federal Republic of
Losel, Walter, Gau-Algesheim, Germany, Federal Republic of
Roos, Otto, Schwabenheim, Germany, Federal Republic of
PA Boehringer Ingelheim KG, Ingelheim am Rhein, Germany, Federal Republic of (non-U.S. corporation)
PI US 5677304 19971014 <--
AI US 1996-649550 19960517 (8)
RLI Division of Ser. No. US 1994-334979, filed on 7 Nov 1994, now patented, Pat. No. US 5565452 which is a continuation of Ser. No. US 1993-81916, filed on 22 Jun 1993, now abandoned
PRAI DE 1992-4220384 19920622
DE 1992-4220361 19920622
DE 1992-4220380 19920622
DT Utility
FS Granted
EXNAM Primary Examiner: Reamer, James H.
LREP Raymond, Robert P., Rieder, Wendy E., Stempel, Alan R.
CLMN Number of Claims: 30
ECL Exemplary Claim: 18
DRWN No Drawings
LN.CNT 982
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to the use of 9-amino-pyridazino-[4',5':3,4]pyrrolo[2,1-a]isoquinolines of the formula ##STR1## and the physiologically acceptable salts thereof with acids, bases and complexing agents for preparing agents for treating chronic inflammatory processes, ulcerative colitis and Crohn's disease, and for producing agents having an antiproliferative activity. The definitions of substituents R.sub.1 to R.sub.9 are given in the specification. The invention also relates to new compounds of general formula I which are also defined in the specification and their use as cerebroprotective agents.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 27 OF 32 USPATFULL on STN
AN 97:91535 USPATFULL
TI Anellated dihydropyridines and the use thereof for the production of pharmaceutical preparations
IN Arndts, Dietrich, Appenheim, Germany, Federal Republic of
Losel, Walter, Gau-Algesheim, Germany, Federal Republic of
Roos, Otto, Schwabenheim, Germany, Federal Republic of
PA Boehringer Ingelheim KG, Ingelheim am Rhein, Germany, Federal Republic of (non-U.S. corporation)
PI US 5674878 19971007 <--
AI US 1995-477214 19950607 (8)
RLI Division of Ser. No. US 1994-249822, filed on 26 May 1994, now abandoned
PRAI DE 1992-4220353 19920622
DE 1992-4220319 19920622
DE 1992-4220355 19920622
DE 1992-4220368 19920622
DE 1992-4220345 19920622
DE 1992-4220312 19920622
DE 1992-4220373 19920622
DE 1992-4220369 19920622
DT Utility
FS Granted
EXNAM Primary Examiner: Ivy, C. Warren; Assistant Examiner: Mach, D. Margaret M.
LREP Raymond, R. P., Devlin, M-E. M., Stempel, A. R.
CLMN Number of Claims: 21
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1935
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compound of general formula I ##STR1## wherein A is a benzo or thieno group;

R.sub.1 is (C.sub.4-6)cycloalkyl, (C.sub.4-6)cycloalkyl-(C.sub.1-5)alkyl or ##STR2## R.sup.2, m, R.sup.3, R.sup.4, R and u are defined as in the specification, and pharmaceutical preparations containing this compound and the new pharmaceutical uses thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 28 OF 32 USPATFULL on STN
AN 97:76139 USPATFULL
TI Annelated dihydropyridines and the use thereof for preparing pharmaceutical preparations
IN Roos, Otto, Schwabenheim, Germany, Federal Republic of
Losel, Walter, Gau Algesheim, Germany, Federal Republic of
Arndts, Dietrich, Appenheim, Germany, Federal Republic of
PA Boehringer Ingelheim KG, Ingelheim am Rhein, Germany, Federal Republic of (non-U.S. corporation)
PI US 5661157 19970826 <--
AI US 1994-360867 19941221 (8)
PRAI DE 1993-4343683 19931221
DT Utility
FS Granted
EXNAM Primary Examiner: Northington Davis, Zinna
LREP Raymond, Robert, Stempel, Alan R., Rieder, Wendy E.
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1201
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compound of general formula I ##STR1## wherein A denotes a benzo, indolo or thienyl group;

B denotes the group --0--, --S-- or --CHR.sup.5 --, wherein R.sup.5 is hydrogen, (C.sub.1-6)alkyl, phenyl or benzyl;

R.sup.3 denotes 2- or 3-thienyl, (C.sub.4-7)cycloalkyl, (C.sub.4-6)cycloalkyl(C.sub.1-5)alkyl or ##STR2## wherein R is (C.sub.1-4)alkyl, hydroxy, --N.sub.3, halogen (F, Cl, Br, I), CF.sub.3 or (C.sub.1-4)alkoxy,

u is 0, 1, 2 or 3, and

m, R.sup.2, R.sup.4, R.sup.7, R.sup.8 and R.sup.9 are as defined in the specification, as well as pharmaceutical preparations containing these compounds and the pharmaceutical use thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 29 OF 32 USPATFULL on STN
AN 97:56685 USPATFULL
TI Anellated dihydropyridines and the use thereof for the production of pharmaceutical preparation
IN Arndts, Dietrich, Appenheim, Germany, Federal Republic of
Losel, Walter, Gau-Algesheim, Germany, Federal Republic of
Roos, Otto, Schwabenheim, Germany, Federal Republic of
PA Boehringer Ingelheim KG, Ingelheim am Rhein, Germany, Federal Republic of (non-U.S. corporation)
PI US 5643919 19970701 <--
AI US 1995-475154 19950607 (8)
RLI Continuation of Ser. No. US 1994-249822, filed on 26 May 1994, now abandoned
PRAI DE 1992-4220369 19920622
DE 1992-4220373 19920622
DE 1992-4220312 19920622
DE 1993-4220368 19930622
DE 1993-4220345 19930622
DE 1993-4220355 19930622
DE 1993-4220319 19930622
DE 1993-4220353 19930622
DT Utility
FS Granted
EXNAM Primary Examiner: Ivy, C. Warren; Assistant Examiner: Mach, D. Margaret M.
LREP Raymond, R. P., Devlin, M-E. M., Stempel, A. R.
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1701
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compound of general formula I ##STR1## wherein A is a benzo or thieno group;

R.sub.1 is (C.sub.4-6)cycloalkyl, (C.sub.4-6)cycloalkyl-(C.sub.1-5)alkyl or ##STR2## R.sup.2, m, R.sup.3, R.sup.4, R and u are defined as in the specification, and pharmaceutical preparations containing this compound and the new pharmaceutical uses thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 30 OF 32 USPATFULL on STN
AN 97:18168 USPATFULL
TI Annelated dihydropyridines and the use thereof for preparing pharmaceutical preparations
IN L osel, Walter, Gau-Algesheim, Germany, Federal Republic of
Roos, Otto, Schwabenheim, Germany, Federal Republic of
Arndts, Dietrich, Appenheim, Germany, Federal Republic of

PA Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany, Federal Republic of (non-U.S. corporation)
PI US 5607943 19970304 <--
AI US 1994-360524 19941221 (8)
PRAI DE 1993-4343684 19931221
DE 1993-4343641 19931221
DT Utility
FS Granted
EXNAM Primary Examiner: Shah, Mukund J.; Assistant Examiner: Wong, King Lit
LREP Raymond, Robert P., Rieder, Wendy E., Devlin, Mary-Ellen M.
CLMN Number of Claims: 3
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 998
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A compound of formula I ##STR1## wherein A denotes a benzo, indolo or thieno group;

R.sup.1 denotes thienyl or the group ##STR2## wherein

R.sup.7, R.sup.8 and R.sup.9 independently of one another may represent methyl, ethyl, propyl, phenyl or benzyl, whilst not more than 2 of the substituents can simultaneously represent phenyl or benzyl;

R.sup.2, m, R.sup.3 and R.sup.4 are defined as in the specification, as well as pharmaceutical preparations containing this compound and the new pharmaceutical uses thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 31 OF 32 USPATFULL on STN
AN 96:94582 USPATFULL
TI 9-amino-pyridazino[4',5':3,4]pyrrolo-[2,1-A]isoquinolines and the use thereof for the production of pharmaceutical preparations
IN Arndts, Dietrich, Appenheim, Germany, Federal Republic of
L osel, Walter, Gau-Algesheim, Germany, Federal Republic of
Roos, Otto, Schwabenheim, Germany, Federal Republic of
PA Boehringer Ingelheim KG, Ingelheim am Rhein, Germany, Federal Republic of (non-U.S. corporation)
PI US 5565452 19961015 <--
AI US 1994-334979 19941107 (8)
RLI Continuation of Ser. No. US 1993-81916, filed on 22 Jun 1993, now abandoned
PRAI DE 1992-4220380 19920622
DE 1993-4220361 19930622
DE 1993-4220384 19930622
DT Utility
FS Granted
EXNAM Primary Examiner: Reamer, James H.
LREP Raymond, Robert P., Rieder, Wendy E., Stempel, Alan R.
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 902
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to the use of 9-amino-pyridazino-[4', 5':3,4]pyrrolo[2,1-a]isoquinolines of the formula ##STR1## and the physiologically acceptable salts thereof with acids, bases and complexing agents for preparing agents for treating chronic inflammatory processes, ulcerative colitis and Crohn's disease, and for producing agents having an antiproliferative activity. The definitions of substituents R.sub.1 to R.sub.9 are given in the specification. The invention also relates to new compounds of general formula I which are also defined in the specification and their use as cerebroprotective

agents.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L27 ANSWER 32 OF 32 TOXCENTER COPYRIGHT 2004 ACS on STN
AN 1997:148269 TOXCENTER
CP Copyright 2004 ACS
DN CA12619251066R
TI Preparation of furanones as **endothelin antagonists**
AU Cheng, Xue-Min; Doherty, Annette Marian; Patt, William Chester; Repine, Joseph Thomas
CS ASSIGNEE: Warner-Lambert Company
PI WO 978169 A1 6 Mar 1997
SO (**1997**) PCT Int. Appl., 46 pp.
CODEN: PIXXD2.
CY UNITED STATES
DT Patent
FS CAPLUS
OS CAPLUS 1997:276449
LA English
ED Entered STN: 20011116
Last Updated on STN: 20040817
AB Novel nonpeptide antagonists of endothelin [I; R1 = (un)substituted C3-12 cycloalkyl, Ph, naphthyl, heteroaryl; R2 = (un)substituted C1-12 alkyl, C3-12 cycloalkyl; R3 = (un)substituted C1-12 alkyl, C3-12 cycloalkyl, etc.; R4 = OH, O(C1-7 alkyl), SH, etc.; X = O, S], useful in treating elevated levels of endothelin, acute and chronic renal failure, hypertension, myocardial infarction, myocardial ischemia, cerebral vasospasm, cerebral ischemia, cerebral infarction, cirrhosis, septic shock, congestive heart failure, endotoxic shock, subarachnoid hemorrhage, arrhythmias, asthma, preeclampsia, atherosclerotic disorders including Raynaud's disease and restenosis, angina, **cancer**, pulmonary hypertension, ischemic disease, gastric mucosal damage, hemorrhagic shock, ischemic bowel disease, stroke, benign prostatic hyperplasia (BPH), and diabetes, were prepared Thus, treatment of 3-(benzo[1,3]dioxol-5-yl)-5-hydroxy-5-(4-methoxyphenyl)-4-(3,4,5-trimethoxybenzyl)-5H-furan-2-one with CF3COOH followed by addition Et3SiH afforded II which showed IC50 of 30 nM against endothelin receptor ETA (ERBA-A) and of > 2500 nM against ETB (ERBA-B).

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